Access DB# _____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Jeff Russel Examiner #: 62705 Date: 11-2-2000
Art Unit: 1653 Phone Number 308-3975 Serial Number: 09/581,044
Mail Box and Bldg/Room Location: CM1-10C01/CM1-9807 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

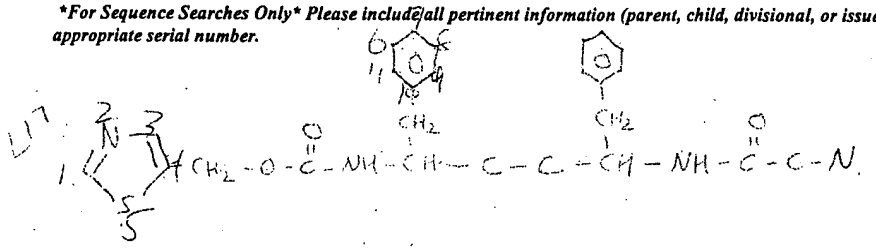
Title of Invention: _____

Inventors (please provide full names): _____

_____

Earliest Priority Filing Date: _____

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**



Broader structural searches have already been done in the parent PCT (PCT/US98/25961 wo 99/29311 application, so there is no need to broaden these searches if you don't find anything.

Thank you.

Edward Hart
Technical Info Specialist
STIC / Biotech
CM1 12C14 Tel: 305-9203

****

STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher: _____	NA Sequence (#)_____	(STN) _____
Searcher Phone #: _____	AA Sequence (#)_____	Dialog _____
Searcher Location: _____	Structure (#) _____	Questel/Orbit _____
Date Searcher Picked Up: 11/2/00	Bibliographic _____	Dr.Link _____
Date Completed: 11/6/00	Litigation _____	Lexis/Nexis _____
Searcher Prep & Review Time: _____	Fulltext _____	Sequence Systems _____
Clerical Prep Time: _____	Patent Family _____	WWW/Internet _____
Online Time: _____	Other _____	Other (specify)_____

PTO-1590 (1-2000)

Access DB# 28382

SEARCH REQUEST FORM

Scientific and Technical Inf rmation Center

Requester's Full Name: Jeff Russel Examiner #: 62785 Date: 11.2-2000
Art Unit: 1653 Phone Number 305-3975 Serial Number: 09/581,049
Mail Box and Bldg/Room Location: CM1-10C01/CM1 9B07 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: HIV/FIV Protease Inhibitors Having A Small P3 Residue

Inventors (please provide full names): Taekyu Lee, Chi-Huey Wong, John Elder

Earliest Priority Filing Date: 12-8-3/1998

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

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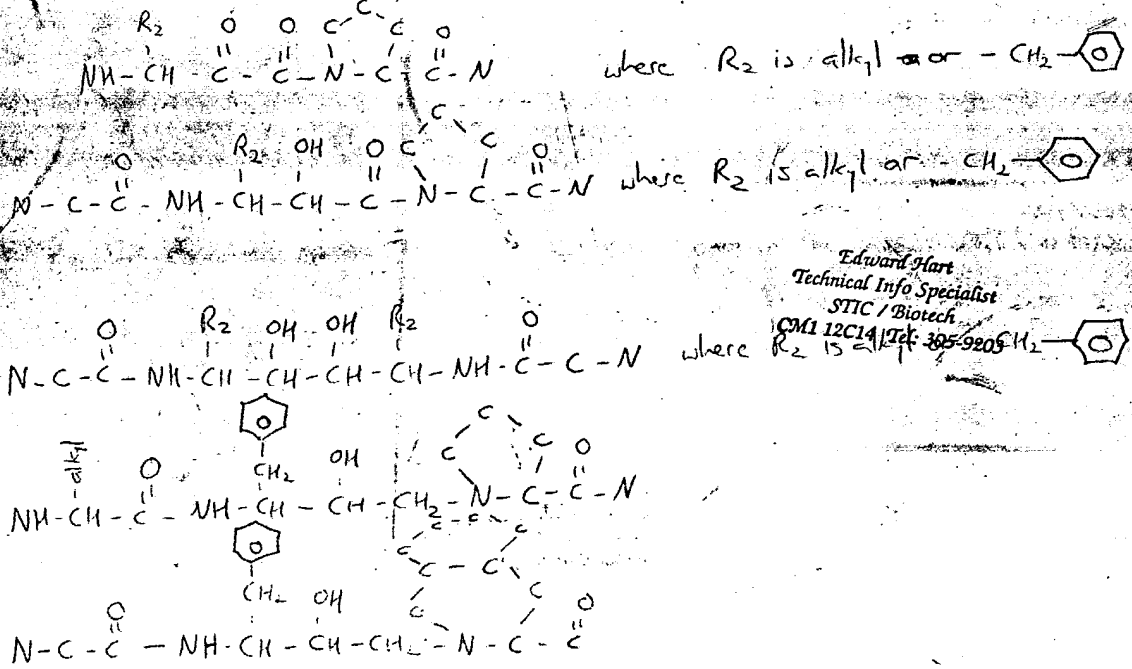

Edward Hart
Technical Info Specialist
STIC / Biotech
CM1 12C14 Tel: 305-9205

****

STAFF USE ONLY

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Searcher Phone #: _____
Searcher Location: _____
Date Searcher Picked Up: 11/2/00
Date Completed: 11/6/00
Searcher Prep & Review Time: _____
Clerical Prep Time: _____
Online Time: _____

Type of Search

NA Sequence (#) _____
AA Sequence (#) _____
Structure (#) _____
Bibliographic _____
Litigation _____
Fulltext _____
Patent Family _____
Other _____

Vendors and cost where applicable

STN _____
Dialog _____
Questel/Orbit _____
Dr.Link _____
Lexis/Nexis _____
Sequence Systems _____
WWW/Internet _____
Other (specify) _____

PTO-1590 (1-2000)

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	1.26	661.41

FILE 'CAPLUS' ENTERED AT 12:04:47 ON 06 NOV 2000
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1967 - 6 Nov 2000 VOL 133 ISS 20
FILE LAST UPDATED: 5 Nov 2000 (20001105/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

Now you can extend your author, patent assignee, patent information, and title searches back to 1907. The records from 1907-1966 now have this searchable data in CAOLD. You now have electronic access to all of CA: 1907 to 1966 in CAOLD and 1967 to the present in CAPLUS on STN.

=> d stat que

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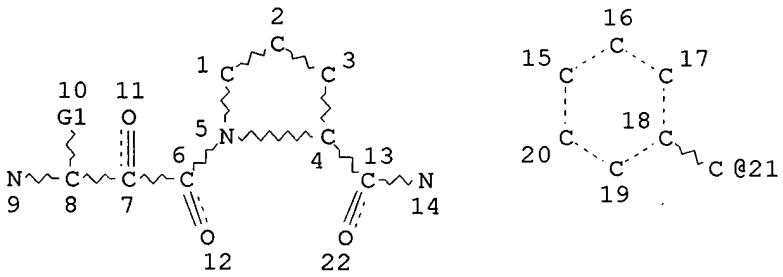

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DEFAULT ECLEVEL IS LIMITED

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NUMBER OF NODES IS 22

STEREO ATTRIBUTES: NONE
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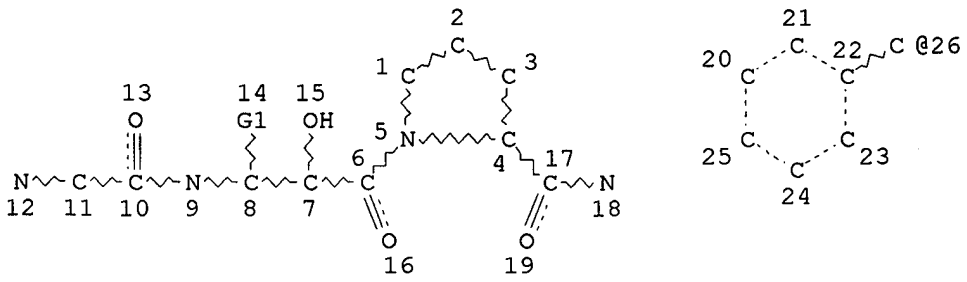

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DEFAULT MLEVEL IS ATOM
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RING(S) ARE ISOLATED OR EMBEDDED
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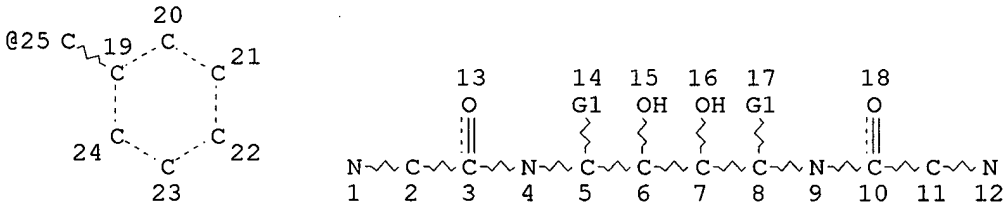
STEREO ATTRIBUTES: NONE
L7 STR



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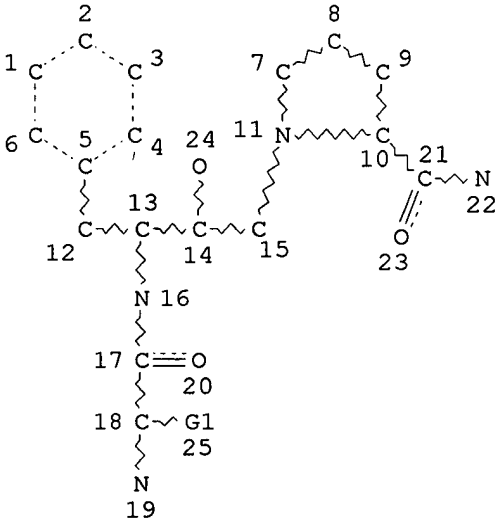
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE
L11 STR



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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
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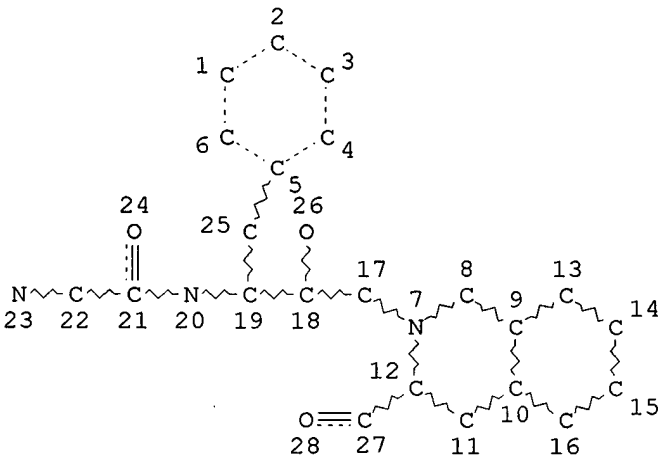
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE
L15 STR



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GRAPH ATTRIBUTES:
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STEREO ATTRIBUTES: NONE
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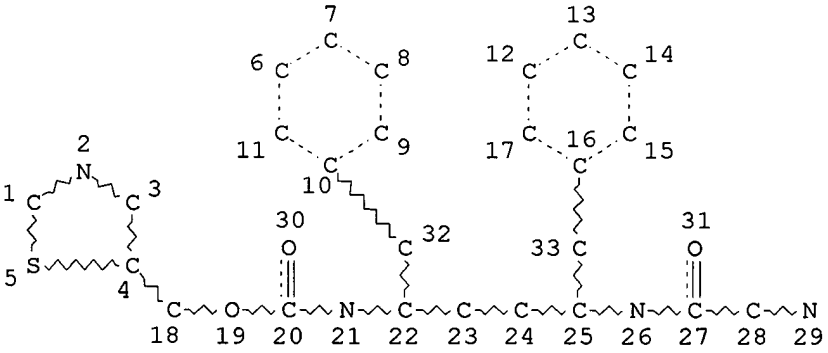

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GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 33

STEREO ATTRIBUTES: NONE

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L22         370 SEA FILE=REGISTRY SUB=L20 SSS FUL L5
L23         390 SEA FILE=REGISTRY SUB=L20 SSS FUL L7
L24          32 SEA FILE=REGISTRY SUB=L20 SSS FUL L11
L25         168 SEA FILE=REGISTRY SUB=L20 SSS FUL L15
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                AND L31 AND L32

=> d ibib abs hitrn 133 tot

L33  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2000 ACS
ACCESSION NUMBER:         1999:390367  CAPLUS
DOCUMENT NUMBER:          131:45104
TITLE:                    HIV/FIV protease inhibitors having a small P3 residue
INVENTOR(S):              Lee, Taekyu; Wong, Chi-Huey; Elder, John H.
PATENT ASSIGNEE(S):       The Scripps Research Institute, USA
SOURCE:                   PCT Int. Appl., 93 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
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     WO 9929311         A1   19990617       WO 1998-US25964  19981208
         W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
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             KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX,
             NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
             UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
             FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
             CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     AU 9919045         A1   19990628       AU 1999-19045    19981208
     EP 1039886         A1   20001004       EP 1998-963800   19981208
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
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PRIORITY APPLN. INFO.:                      US 1997-67959    19971208
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OTHER SOURCE(S):          MARPAT 131:45104
GI
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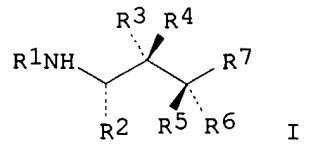

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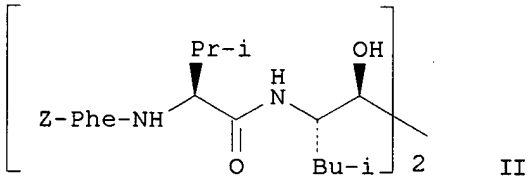

II

AB Protease inhibitors I [R1 = H, carbobenzyloxy (Z), Z-Val, Z-protected dipeptidyl; R2 = benzyl, isobutyl; R3, R4 H, H; H, OH, O; R5, R6 = H, H; O; R7 = prolinamide or N-tert-butylprolinamide residue] were prepd. Thus, peptidyl diol II was prepd. and showed Ki = 487 .+-. 20 and 5.5 .+-. 0.8 for inhibition of FIV PR and HIV PR, resp.

IT **222848-91-1P 222848-96-6P**
RL: BAC (Biological activity or effector, except adverse); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(HIV/FIV protease inhibitors having a small P3 residue)

IT **129467-48-7P 141197-75-3P 204907-85-7P**
222847-52-1P 222847-65-6P 222848-86-4P
222849-10-7P 222849-11-8P 227317-37-5P
227317-40-0P 227317-41-1P 227317-42-2P
227317-43-3P 227317-44-4P 227317-45-5P
227317-46-6P 227317-47-7P 227317-48-8P
227317-49-9P 227317-50-2P 227317-51-3P
227317-52-4P 227317-53-5P 227317-54-6P
227317-55-7P 227317-56-8P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(HIV/FIV protease inhibitors having a small P3 residue)

IT **204910-66-7 222847-47-4**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HIV/FIV protease inhibitors having a small P3 residue)

IT **204907-84-6P 204907-86-8P 222847-60-1P**
222847-71-4P 222847-74-7P 222849-07-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(HIV/FIV protease inhibitors having a small P3 residue)

REFERENCE COUNT: 10
REFERENCE(S):
(1) Abbott Laboratories; WO 9323361 A1 1993 CAPLUS
(2) Baker; US 5541321 A 1996
(3) Dreyer; Biochemistry 1993, V32(3), P937 CAPLUS
(6) Japan Energy Corporation Tokyo-To; EP 0751145 A2 1997 CAPLUS
(10) Tien; US 5567823 A 1996 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:73185 CAPLUS
DOCUMENT NUMBER: 130:276229
TITLE: Development of a New Type of Protease Inhibitors, Efficacious against FIV and HIV Variants
AUTHOR(S): Lee, Taekyu; Le, Van-Duc; Lim, Dongyeol; Lin, Ying-Chuan; Morris, Garrett M.; Wong, Andrew L.; Olson, Arthur J.; Elder, John H.; Wong, Chi-Huey
CORPORATE SOURCE: Department of Chemistry and the Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: J. Am. Chem. Soc. (1999), 121(6), 1145-1155
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Based on the structural anal. of FIV protease and drug-resistant HIV proteases and mol. modeling, a new type of inhibitors with a small P3 residue has been developed. These inhibitors are effective against HIV and its drug-resistant mutants, as well as SIV and FIV. Modification of existing HIV protease inhibitors by reducing the size of the P3 residue has the same effect. This finding provides a new strategy for the development of HIV protease inhibitors effective against the wild-type and drug-resistant mutants. It further supports the use of FIV protease as a useful model for drug-resistant HIV proteases, which often have a more constricted binding region for the P3 group or the combined P3 and P1 groups.
IT **129467-48-7P 191849-89-5P 204907-85-7P**
204907-86-8P 204910-66-7P 222847-47-4P
222847-52-1P 222847-60-1P 222847-65-6P
222847-71-4P 222847-74-7P 222847-79-2P
222847-84-9P 222847-92-9P 222848-86-4P
222848-91-1P 222848-96-6P 222849-01-6P
222849-07-2P 222849-10-7P 222849-11-8P
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis of a new type of protease inhibitors, efficacious against FIV and HIV variants)
IT **127779-20-8**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis of a new type of protease inhibitors, efficacious against FIV and HIV variants)
REFERENCE COUNT: 34
REFERENCE(S):
(1) Babine, R; Chem Rev 1997, V97, P1359 CAPLUS
(2) Bacheler, L; Antiviral Chem Chemother 1994, V5, P111 CAPLUS
(3) Budt, K; Bioorg Med Chem 1995, V3, P559 CAPLUS
(4) Condra, J; Nature 1995, V374, P569 CAPLUS
(5) De Lucca, G; Drug Discovery Today 1997, V2, P6 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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E1 THROUGH E42 ASSIGNED

=> d his l34

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SEL HIT RN

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L34 ANSWER 1 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **227317-56-8** REGISTRY
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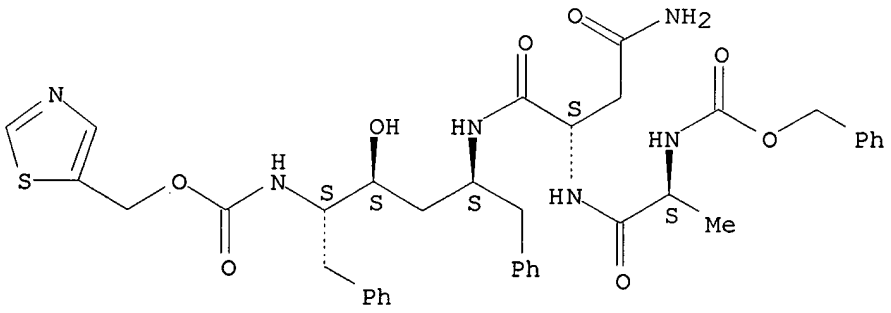
MF C38 H44 N6 O8 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

L34 ANSWER 2 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **227317-55-7** REGISTRY
CN L-Valinamide, N-[(phenylmethoxy)carbonyl]-L-valyl-N-[(1S,3S,4S)-3-hydroxy-5-phenyl-1-(phenylmethyl)-4-[[(5-thiazolylmethoxy)carbonyl]amino]pentyl]- (9CI) (CA INDEX NAME)
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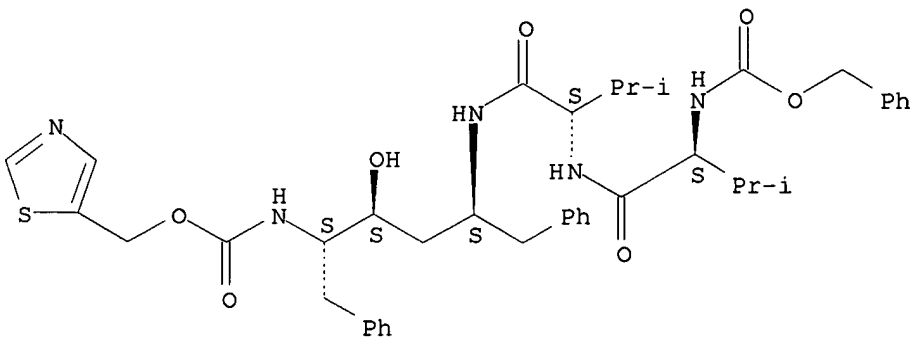
MF C41 H51 N5 O7 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



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1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

L34 ANSWER 3 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **227317-54-6** REGISTRY
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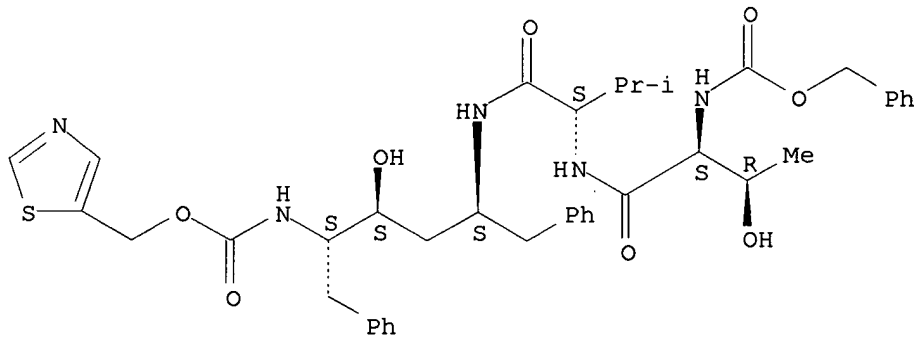
MF C40 H49 N5 O8 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



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1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

L34 ANSWER 4 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **227317-53-5** REGISTRY
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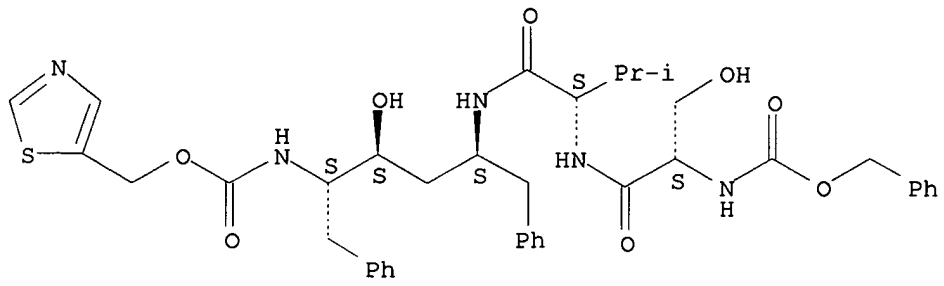

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1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

L34 ANSWER 5 OF 42 REGISTRY COPYRIGHT 2000 ACS
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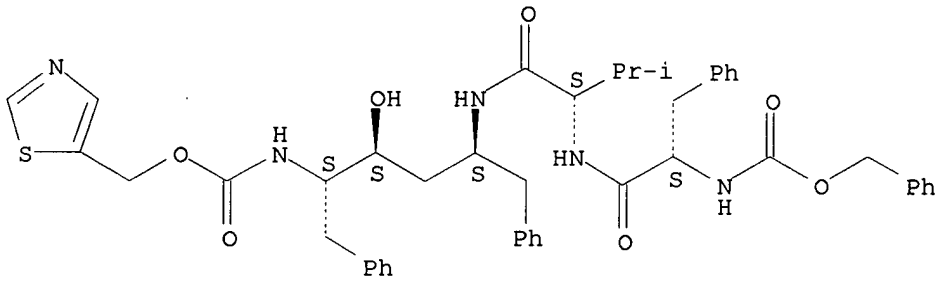
Absolute stereochemistry.



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

L34 ANSWER 6 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **227317-51-3** REGISTRY
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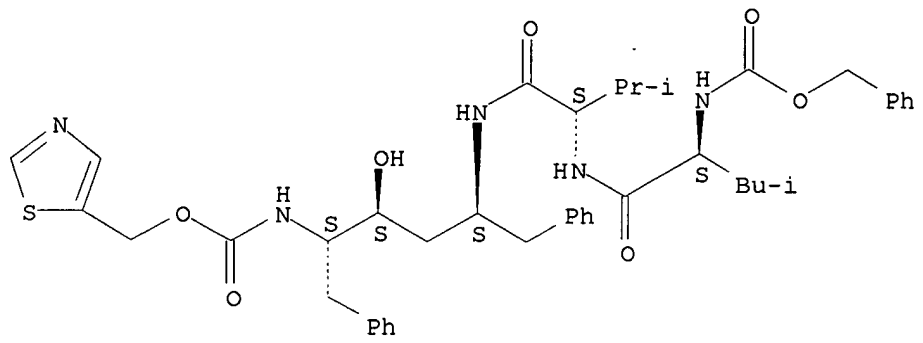
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

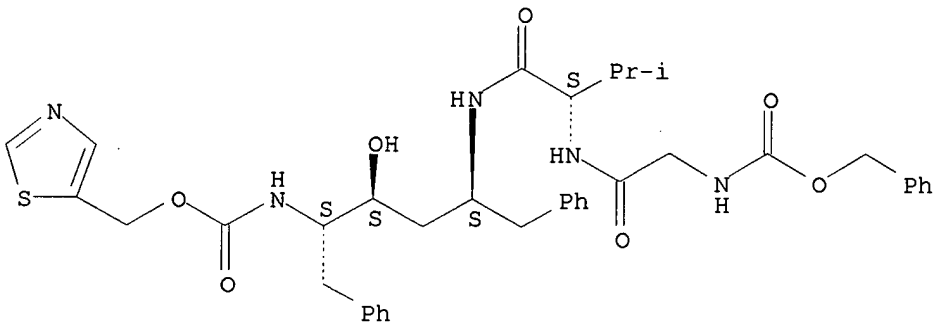


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

L34 ANSWER 7 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **227317-50-2** REGISTRY
CN L-Valinamide, N-[(phenylmethoxy)carbonyl]glycyl-N-[(1S,3S,4S)-3-hydroxy-5-phenyl-1-(phenylmethyl)-4-[[(5-thiazolylmethoxy)carbonyl]amino]pentyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C38 H45 N5 O7 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

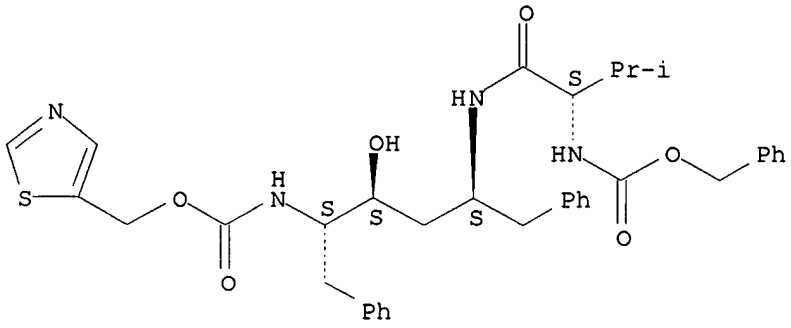


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

L34 ANSWER 8 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **227317-49-9** REGISTRY
CN 2-Oxa-4,7,12-triazatridecan-13-oic acid, 10-hydroxy-5-(1-methylethyl)-3,6-dioxo-1-phenyl-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (5S,8S,10S,11S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C36 H42 N4 O6 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

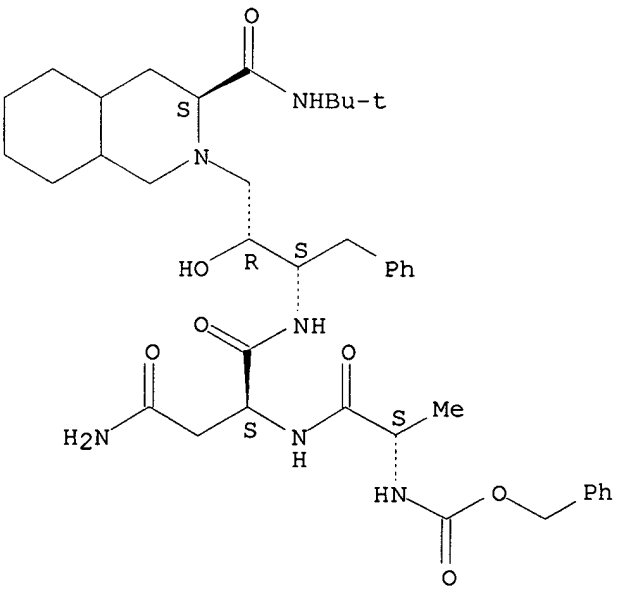


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

L34 ANSWER 9 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **227317-48-8** REGISTRY
CN L-Aspartamide, N-[(phenylmethoxy)carbonyl]-L-alanyl-N-[(1S,2R)-3-[(3S)-3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C39 H56 N6 O7
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



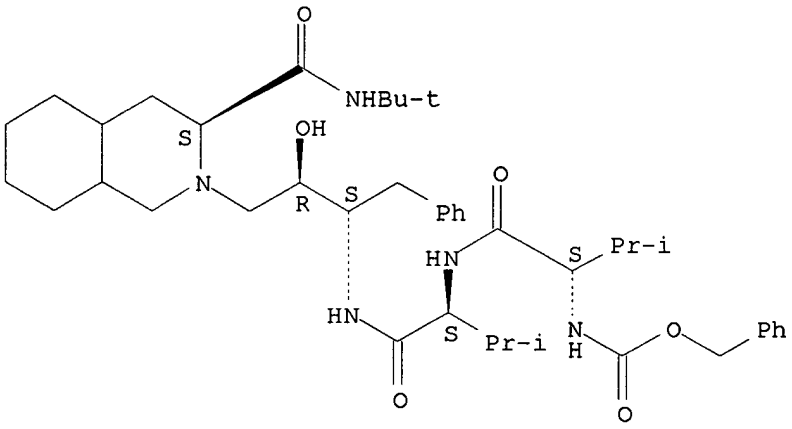
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

L34 ANSWER 10 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **227317-47-7** REGISTRY

CN L-Valinamide, N-[(phenylmethoxy)carbonyl]-L-valyl-N-[(1S,2R)-3-[(3S)-3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C42 H63 N5 O6
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

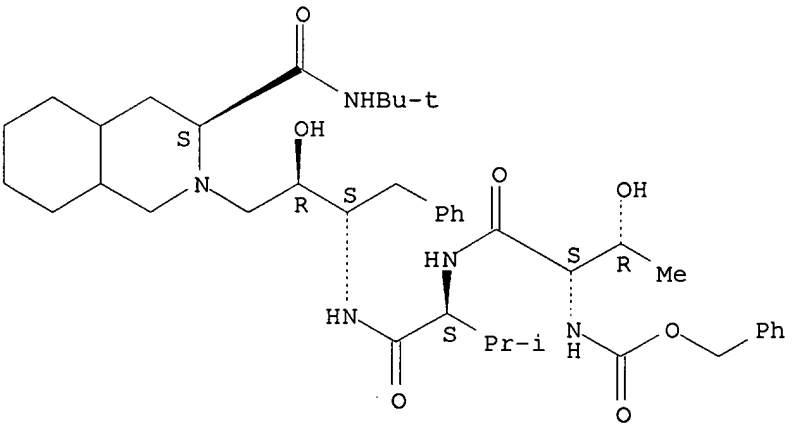


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

L34 ANSWER 11 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **227317-46-6** REGISTRY
CN L-Valinamide, N-[(phenylmethoxy)carbonyl]-L-threonyl-N-[(1S,2R)-3-[(3S)-3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C41 H61 N5 O7
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

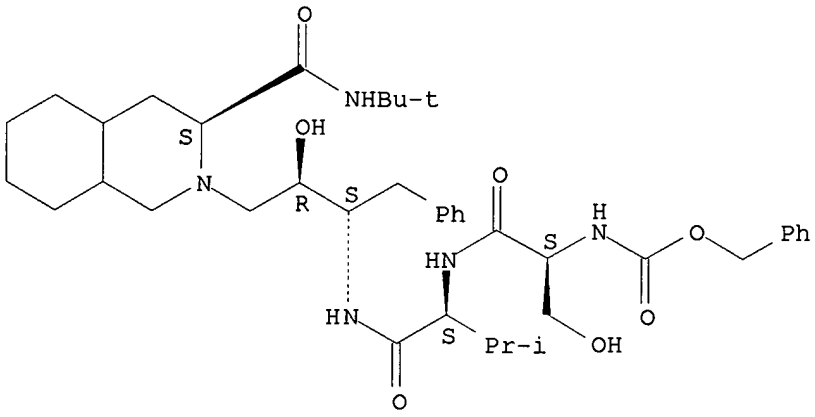


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

L34 ANSWER 12 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **227317-45-5** REGISTRY
CN L-Valinamide, N-[(phenylmethoxy)carbonyl]-L-seryl-N-[(1S,2R)-3-[(3S)-3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C40 H59 N5 O7
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

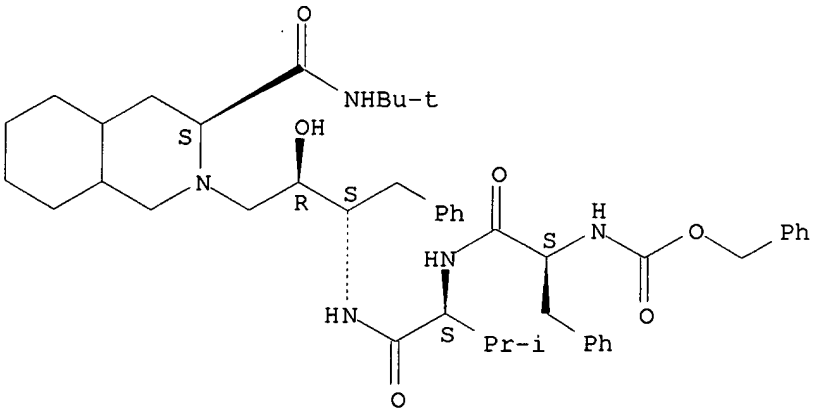


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

L34 ANSWER 13 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **227317-44-4** REGISTRY
CN L-Valinamide, N-[(phenylmethoxy)carbonyl]-L-phenylalanyl-N-[(1S,2R)-3-[(3S)-3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C46 H63 N5 O6
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

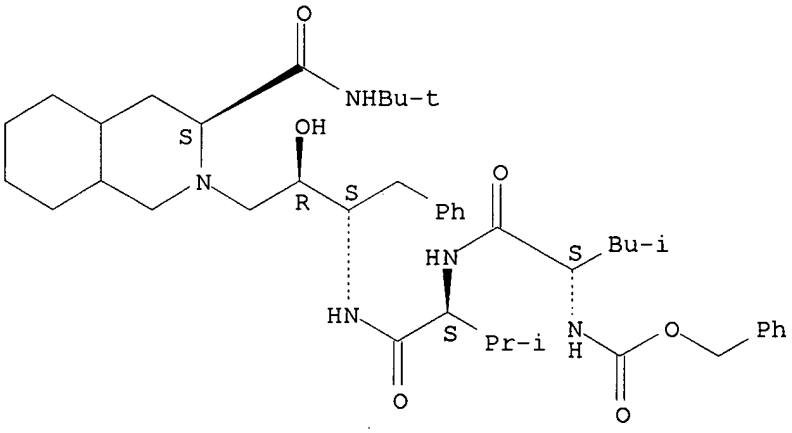


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

L34 ANSWER 14 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **227317-43-3** REGISTRY
CN L-Valinamide, N-[(phenylmethoxy)carbonyl]-L-leucyl-N-[(1S,2R)-3-[(3S)-3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C43 H65 N5 O6
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

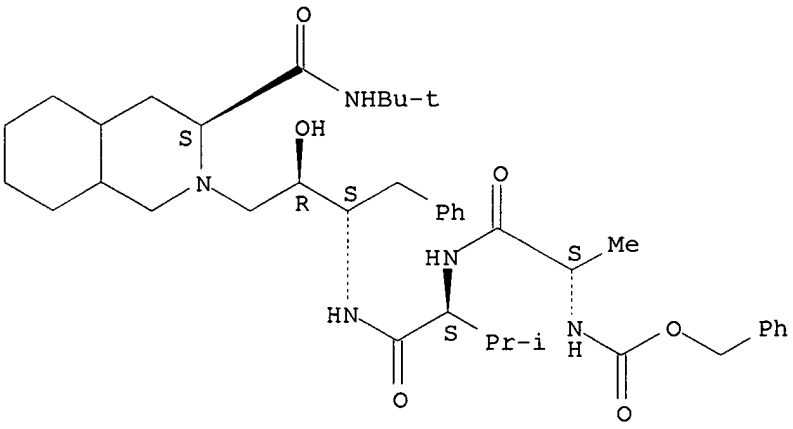


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

L34 ANSWER 15 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **227317-42-2** REGISTRY
CN L-Valinamide, N-[(phenylmethoxy)carbonyl]-L-alanyl-N-[(1S,2R)-3-[(3S)-3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C40 H59 N5 O6
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

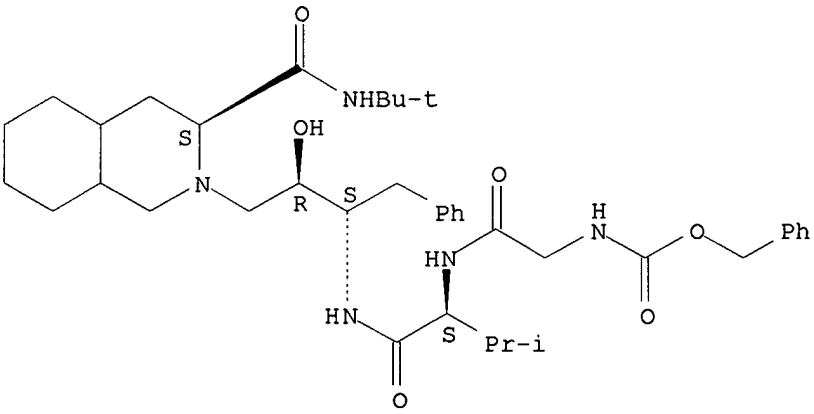


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

L34 ANSWER 16 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **227317-41-1** REGISTRY
CN L-Valinamide, N-[(phenylmethoxy)carbonyl]glycyl-N-[(1S,2R)-3-[(3S)-3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C39 H57 N5 O6
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



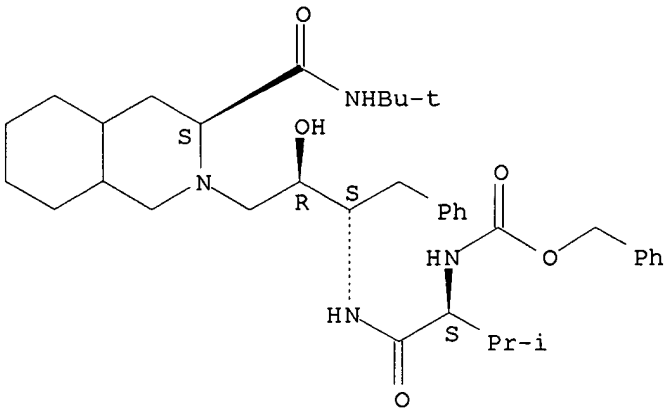
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

L34 ANSWER 17 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **227317-40-0** REGISTRY
CN Carbamic acid, [(1S)-1-[[[(1S,2R)-3-[(3S)-3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]amino]carbonyl]-2-methylpropyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)
FS STEREOSEARCH

MF C37 H54 N4 O5
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

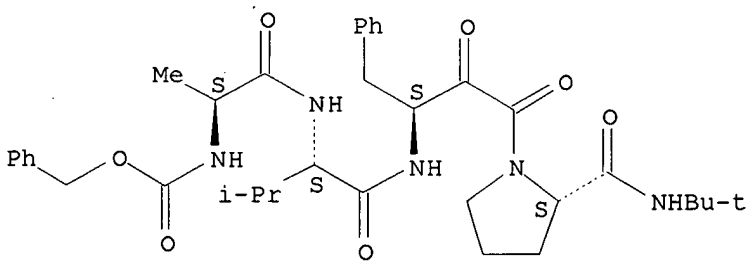


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

L34 ANSWER 18 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **227317-37-5** REGISTRY
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-L-alanyl-L-valyl-(.beta.S)-.beta.-amino-.alpha.-oxobenzenebutanoyl-N-(1,1-dimethylethyl)- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C35 H47 N5 O7
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



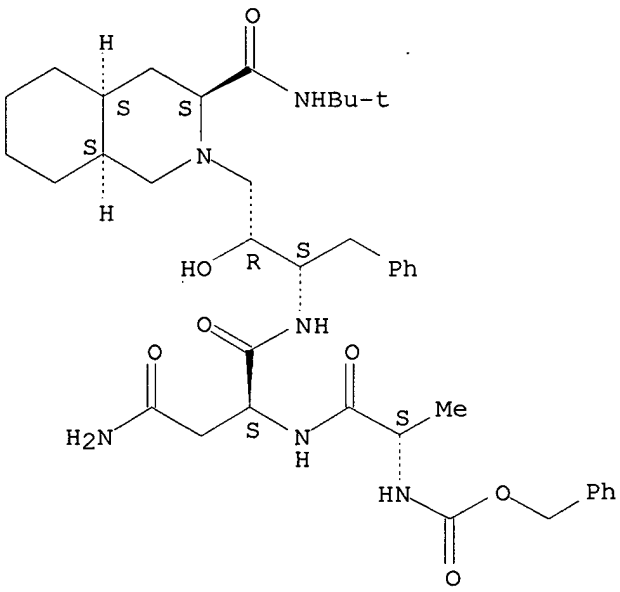
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

L34 ANSWER 19 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **222849-11-8** REGISTRY
CN L-Aspartamide, N-[(phenylmethoxy)carbonyl]-L-alanyl-N1-[(1S,2R)-3-[(3S,4aS,8aS)-3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN TL 4 (peptide)
FS STEREOSEARCH

MF C39 H56 N6 O7
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

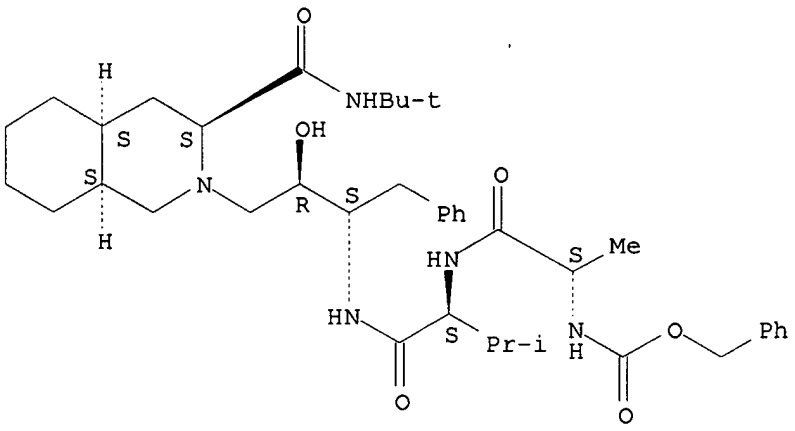
REFERENCE 1: 133:131676

REFERENCE 2: 131:45104

REFERENCE 3: 130:276229

L34 ANSWER 20 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **222849-10-7** REGISTRY
CN L-Valinamide, N-[(phenylmethoxy)carbonyl]-L-alanyl-N-[(1S,2R)-3-[(3S,4aS,8aS)-3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN TL 5 (peptide)
FS STEREOSEARCH
MF C40 H59 N5 O6
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

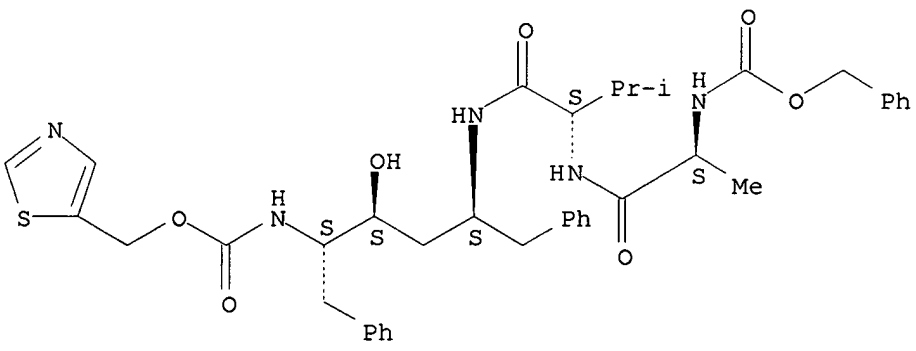
REFERENCE 1: 133:131676

REFERENCE 2: 131:45104

REFERENCE 3: 130:276229

L34 ANSWER 21 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **222849-07-2** REGISTRY
CN L-Valinamide, N-[(phenylmethoxy)carbonyl]-L-alanyl-N-[(1S,3S,4S)-3-hydroxy-5-phenyl-1-(phenylmethyl)-4-[[(5-thiazolylmethoxy)carbonyl]amino]pentyl]-(9CI) (CA INDEX NAME)
OTHER NAMES:
CN VL 346
FS STEREOSEARCH
MF C39 H47 N5 O7 S
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

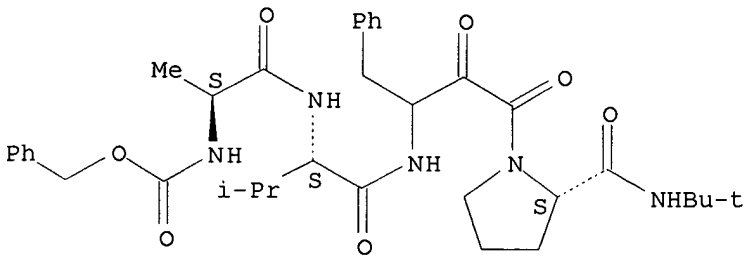
REFERENCE 1: 133:131676

REFERENCE 2: 131:45104

REFERENCE 3: 130:276229

L34 ANSWER 22 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **222849-01-6** REGISTRY
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-L-alanyl-L-valyl-.beta.-amino-.alpha.-oxobenzenebutanoyl-N-(1,1-dimethylethyl)- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C35 H47 N5 O7
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.

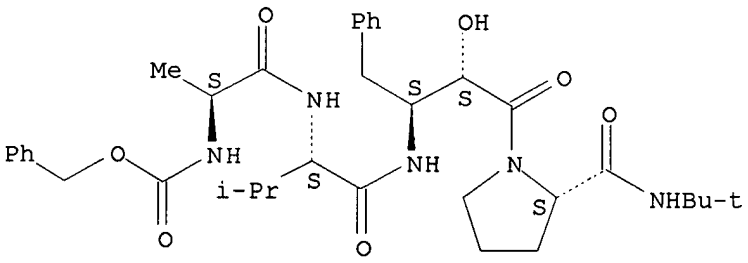


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:276229

L34 ANSWER 23 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **222848-96-6** REGISTRY
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-L-alanyl-L-valyl-(.alpha.S,.beta.S)-.beta.-amino-.alpha.-hydroxybenzenebutanoyl-N-(1,1-dimethylethyl)- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C35 H49 N5 O7
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

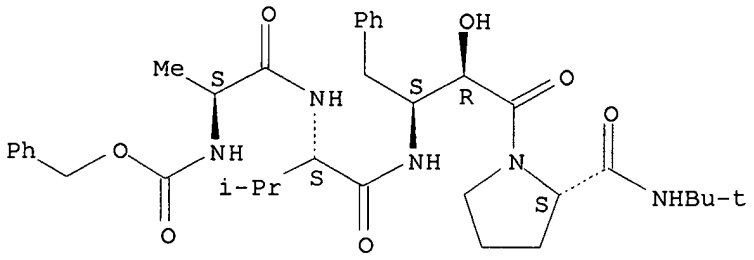
REFERENCE 1: 131:45104

REFERENCE 2: 130:276229

L34 ANSWER 24 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **222848-91-1** REGISTRY
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-L-alanyl-L-valyl-(.alpha.R,.beta.S)-.beta.-amino-.alpha.-hydroxybenzenebutanoyl-N-(1,1-dimethylethyl)- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C35 H49 N5 O7

SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



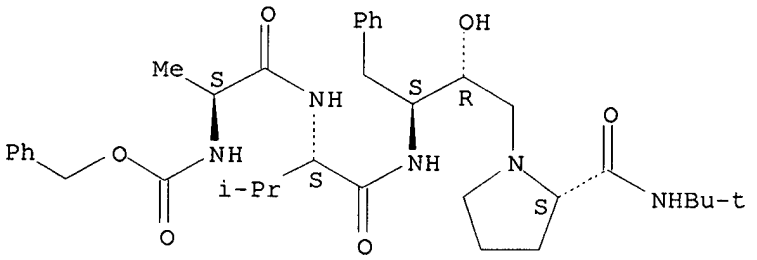
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

REFERENCE 2: 130:276229

L34 ANSWER 25 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **222848-86-4** REGISTRY
CN L-Valinamide, N-[(phenylmethoxy)carbonyl]-L-alanyl-N-[(1S,2R)-3-[(2S)-2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2-hydroxy-1-(phenylmethyl)propyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C35 H51 N5 O6
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



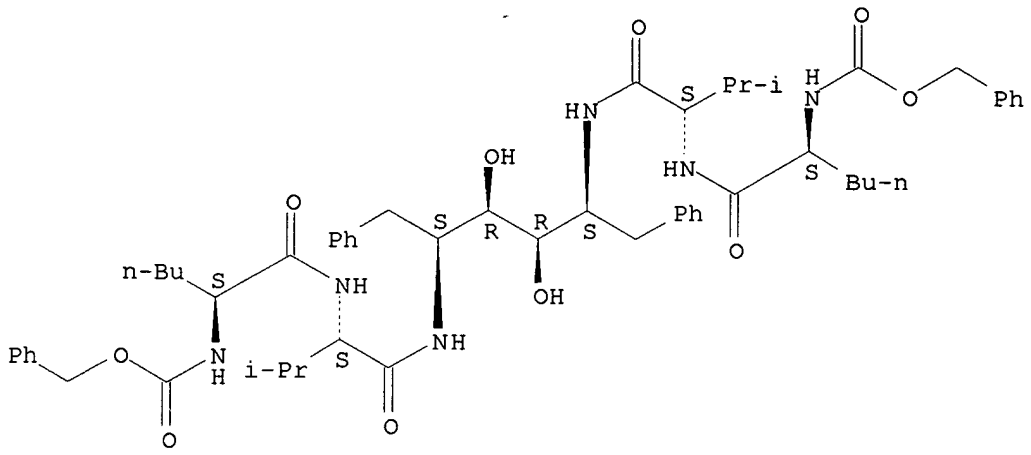
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

REFERENCE 2: 130:276229

L34 ANSWER 26 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **222847-92-9** REGISTRY
CN L-Valinamide, 2,2'-[(1S,2R,3R,4S)-2,3-dihydroxy-1,4-bis(phenylmethyl)-1,4-butanediyl]bis[N-[(phenylmethoxy)carbonyl]-L-norleucyl- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C56 H76 N6 O10
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.

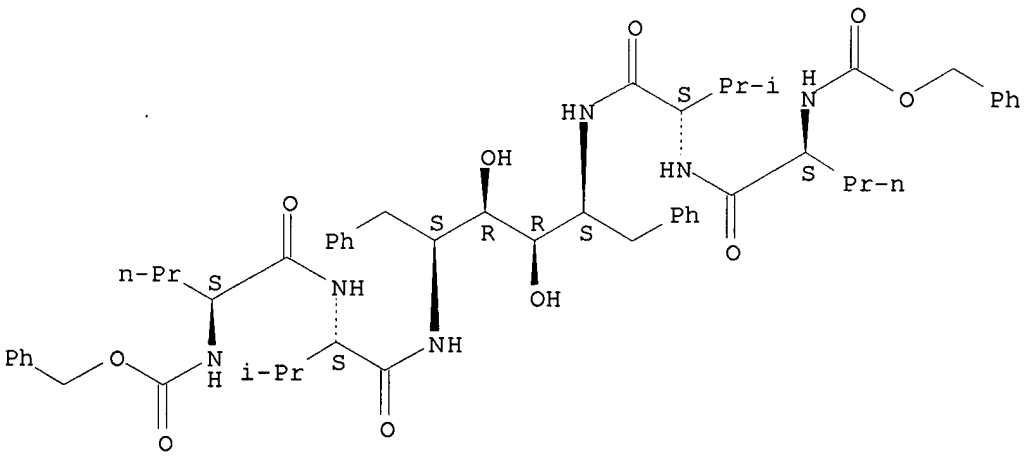


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:276229

L34 ANSWER 27 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **222847-84-9** REGISTRY
CN L-Valinamide, 2,2'-[(1S,2R,3R,4S)-2,3-dihydroxy-1,4-bis(phenylmethyl)-1,4-butanediyl]bis[N-[(phenylmethoxy)carbonyl]-L-norvalyl- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C54 H72 N6 O10
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



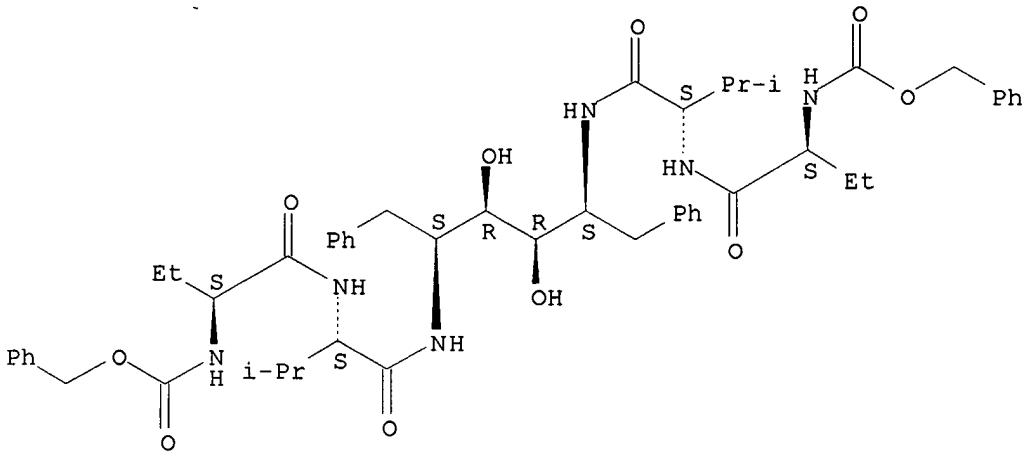
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:276229

L34 ANSWER 28 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **222847-79-2** REGISTRY
CN L-Iditol, 1,2,5,6-tetradeoxy-2,5-bis[[(2S)-3-methyl-1-oxo-2-[[(2S)-1-oxo-2-[[(phenylmethoxy)carbonyl]amino]butyl]amino]butyl]amino]-1,6-diphenyl- (9CI) (CA INDEX NAME)

FS STEREOSEARCH
MF C52 H68 N6 O10
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.

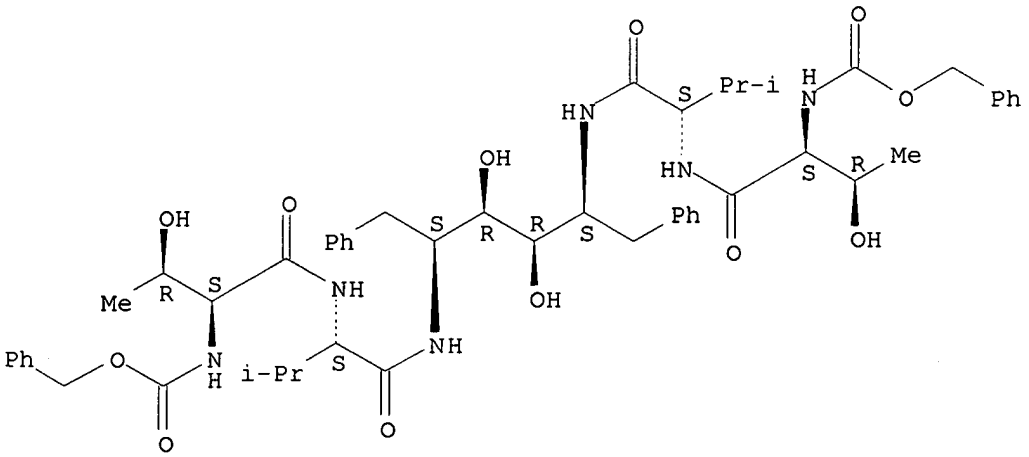


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:276229

L34 ANSWER 29 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **222847-74-7** REGISTRY
CN L-Valinamide, 2,2'-[(1S,2R,3R,4S)-2,3-dihydroxy-1,4-bis(phenylmethyl)-1,4-butanediyl]bis[N-[(phenylmethoxy)carbonyl]-L-threonyl- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C52 H68 N6 O12
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

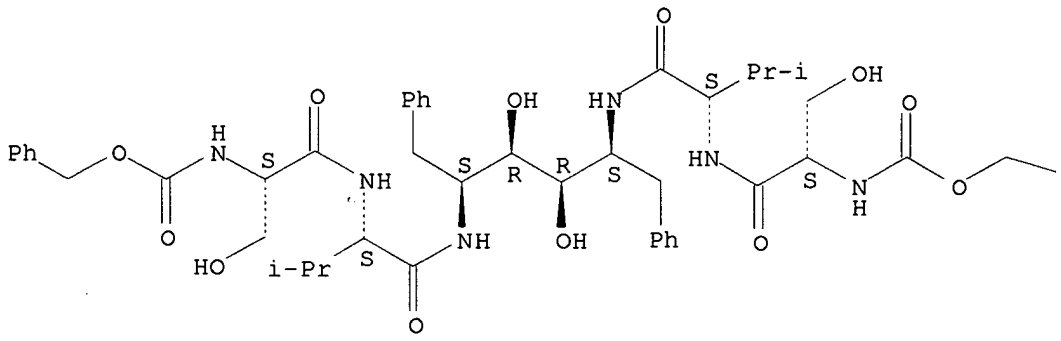
REFERENCE 1: 131:45104

REFERENCE 2: 130:276229

L34 ANSWER 30 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **222847-71-4** REGISTRY
CN L-Valinamide, 2,2'-[(1S,2R,3R,4S)-2,3-dihydroxy-1,4-bis(phenylmethyl)-1,4-butanediyl]bis[N-[(phenylmethoxy)carbonyl]-L-seryl- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C50 H64 N6 O12
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

Ph

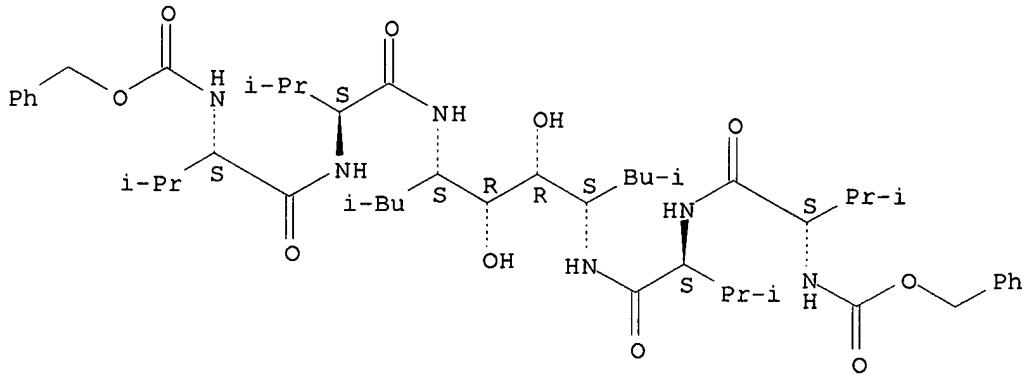
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

REFERENCE 2: 130:276229

L34 ANSWER 31 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **222847-65-6** REGISTRY
CN L-Valinamide, 2,2'-[(1S,2R,3R,4S)-2,3-dihydroxy-1,4-bis(2-methylpropyl)-1,4-butanediyl]bis[N-[(phenylmethoxy)carbonyl]-L-valyl- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C48 H76 N6 O10
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



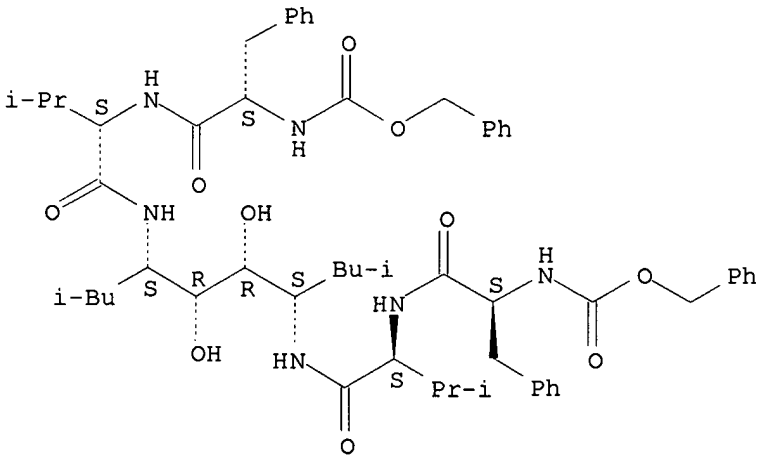
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

REFERENCE 2: 130:276229

L34 ANSWER 32 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **222847-60-1** REGISTRY
CN L-Valinamide, 2,2'-[(1S,2R,3R,4S)-2,3-dihydroxy-1,4-bis(2-methylpropyl)-1,4-butanediyl]bis[N-[(phenylmethoxy)carbonyl]-L-phenylalanyl- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C56 H76 N6 O10
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

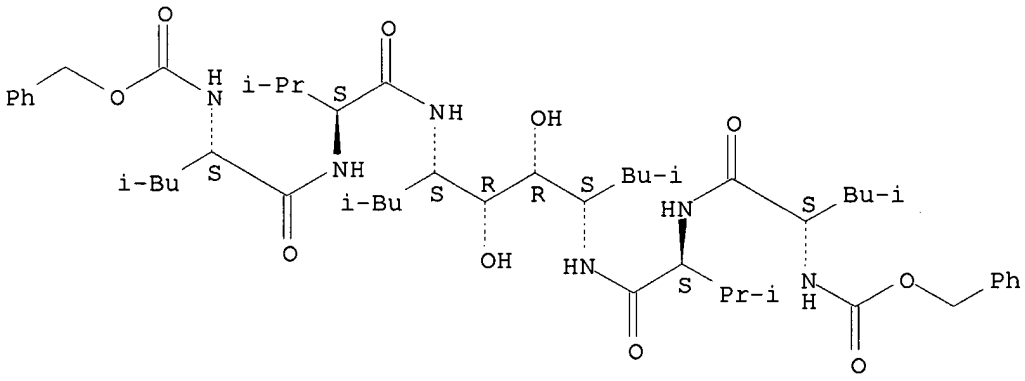
REFERENCE 1: 131:45104

REFERENCE 2: 130:276229

L34 ANSWER 33 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **222847-52-1** REGISTRY
CN L-Valinamide, 2,2'-[(1S,2R,3R,4S)-2,3-dihydroxy-1,4-bis(2-methylpropyl)-1,4-butanediyl]bis[N-[(phenylmethoxy)carbonyl]-L-leucyl- (9CI) (CA INDEX

NAME)
FS STEREOSEARCH
MF C50 H80 N6 O10
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



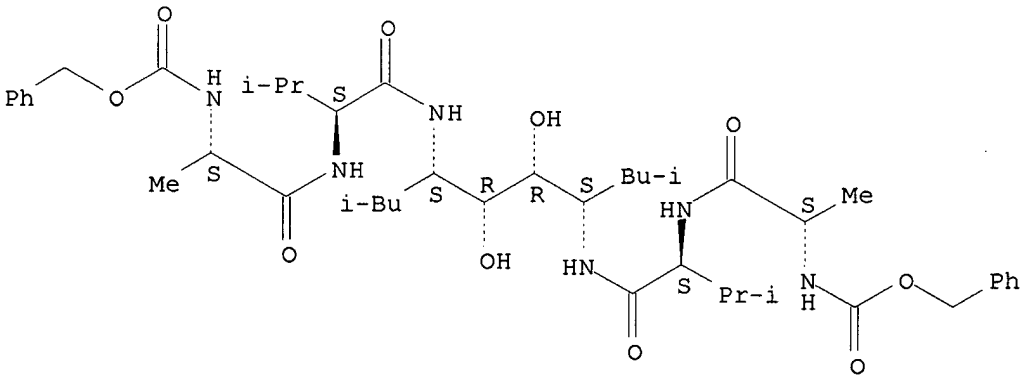
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

REFERENCE 2: 130:276229

L34 ANSWER 34 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **222847-47-4** REGISTRY
CN L-Valinamide, 2,2'-[(1S,2R,3R,4S)-2,3-dihydroxy-1,4-bis(2-methylpropyl)-1,4-butanediyl]bis[N-[(phenylmethoxy)carbonyl]-L-alanyl- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C44 H68 N6 O10
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

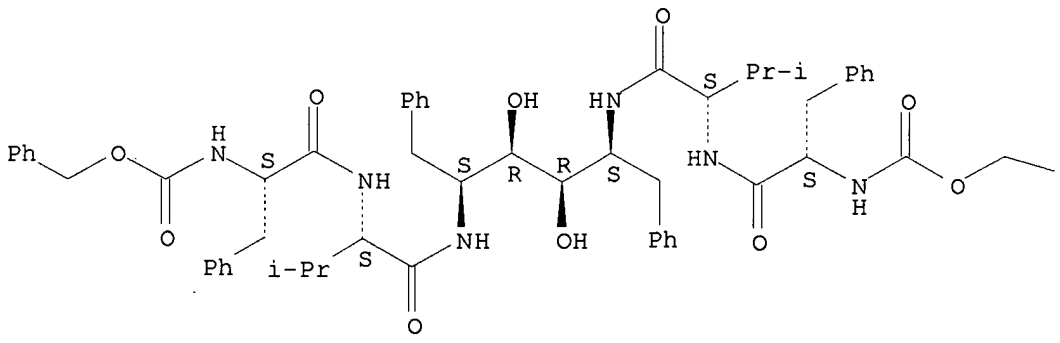
REFERENCE 1: 131:45104

REFERENCE 2: 130:276229

L34 ANSWER 35 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **204910-66-7** REGISTRY
CN L-Iditol, 1,2,5,6-tetradeoxy-1,6-diphenyl-2,5-bis[[N-[(phenylmethoxy)carbonyl]-L-phenylalanyl-L-valyl]amino]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C62 H72 N6 O10
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.

PAGE 1-A



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Ph

3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

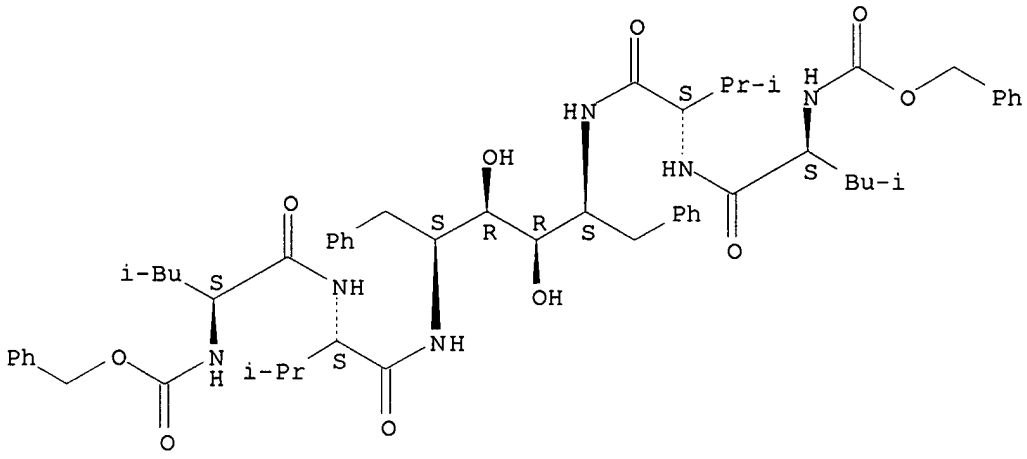
REFERENCE 1: 131:45104

REFERENCE 2: 130:276229

REFERENCE 3: 128:238962

L34 ANSWER 36 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **204907-86-8** REGISTRY
CN L-Iditol, 1,2,5,6-tetradeoxy-1,6-diphenyl-2,5-bis[[N-[(phenylmethoxy)carbonyl]-L-leucyl-L-valyl]amino]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C56 H76 N6 O10
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

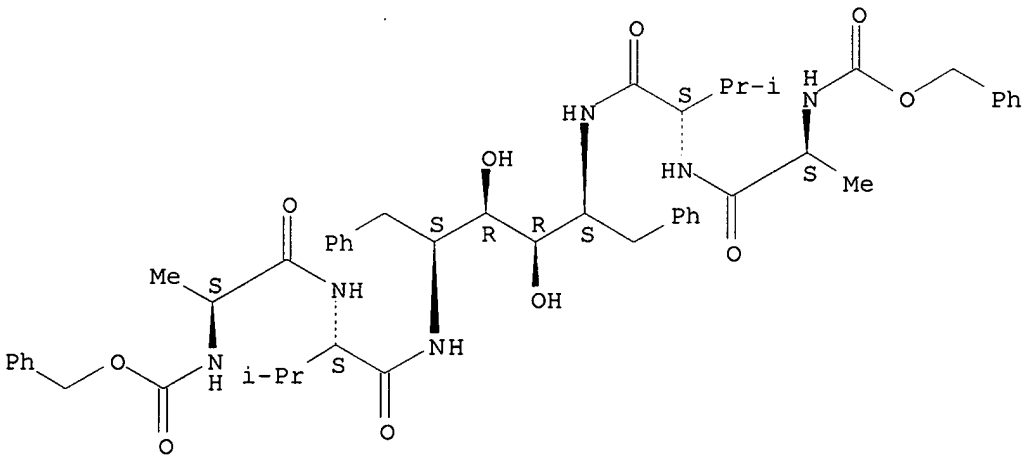
REFERENCE 1: 131:45104

REFERENCE 2: 130:276229

REFERENCE 3: 128:238962

L34 ANSWER 37 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **204907-85-7** REGISTRY
CN L-Iditol, 1,2,5,6-tetradeoxy-1,6-diphenyl-2,5-bis[[N-[(phenylmethoxy)carbonyl]-L-alanyl-L-valyl]amino]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C50 H64 N6 O10
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

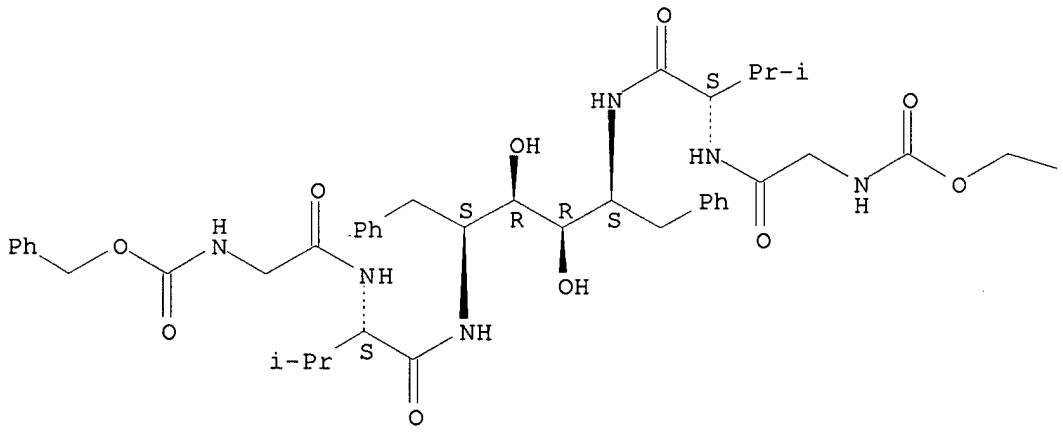
REFERENCE 2: 130:276229

REFERENCE 3: 128:238962

L34 ANSWER 38 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **204907-84-6** REGISTRY
CN L-Iditol, 1,2,5,6-tetradeoxy-1,6-diphenyl-2,5-bis[[N-[(phenylmethoxy)carbonyl]glycyl-L-valyl]amino]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C48 H60 N6 O10
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.

PAGE 1-A



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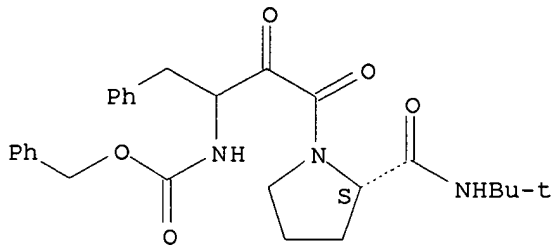
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

REFERENCE 2: 128:238962

L34 ANSWER 39 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **191849-89-5** REGISTRY
CN Carbamic acid, [3-[(2S)-2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, (2S)-
FS STEREOSEARCH
MF C27 H33 N3 O5
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



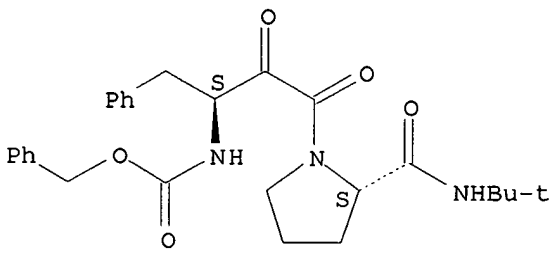
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:276229

REFERENCE 2: 127:81793

L34 ANSWER 40 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **141197-75-3** REGISTRY
CN Carbamic acid, [(1S)-3-[(2S)-2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [S-(R*,R*)]-
FS STEREOSEARCH
MF C27 H33 N3 O5
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, TOXLIT
(*File contains numerically searchable property data)

Absolute stereochemistry.



5 REFERENCES IN FILE CA (1967 TO DATE)
5 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

REFERENCE 2: 124:105570

REFERENCE 3: 120:289408

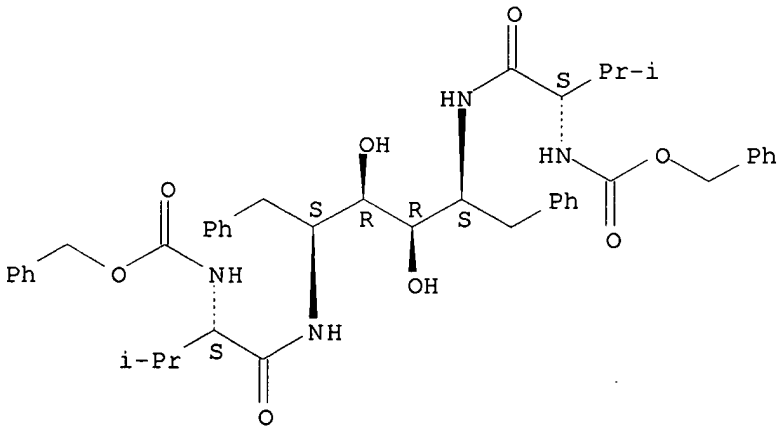
REFERENCE 4: 120:245776

REFERENCE 5: 116:227702

L34 ANSWER 41 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **129467-48-7** REGISTRY
CN L-Iditol, 1,2,5,6-tetradeoxy-2,5-bis[[(2S)-3-methyl-1-oxo-2-

[[(phenylmethoxy)carbonyl]amino]butyl]amino]-1,6-diphenyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Iditol, 1,2,5,6-tetradeoxy-2,5-bis[[3-methyl-1-oxo-2-[[(phenylmethoxy)carbonyl]amino]butyl]amino]-1,6-diphenyl-, [2(S),5(S)]-
OTHER NAMES:
CN A 75925
FS STEREOSEARCH
DR 142861-15-2
MF C44 H54 N4 O8
SR CA
LC STN Files: AIDSLINE, BEILSTEIN*, BIOSIS, CA, CAPLUS, CASREACT, CHEMINFORMRX, DDFU, DRUGU, MEDLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



19 REFERENCES IN FILE CA (1967 TO DATE)
19 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

REFERENCE 2: 130:276229

REFERENCE 3: 128:238962

REFERENCE 4: 128:30075

REFERENCE 5: 127:75549

REFERENCE 6: 124:344059

REFERENCE 7: 121:205978

REFERENCE 8: 119:139718

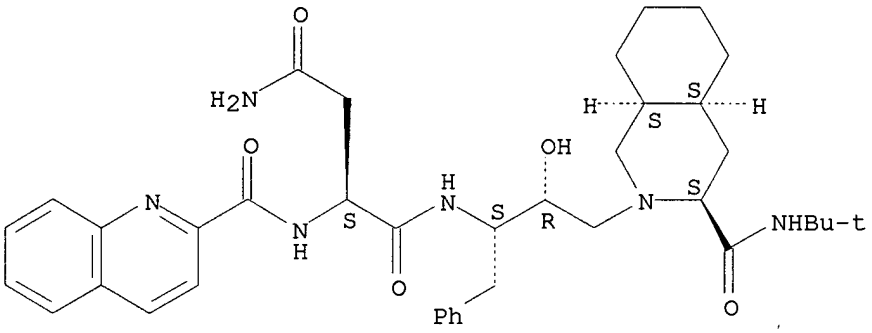
REFERENCE 9: 119:138493

REFERENCE 10: 119:85387

L34 ANSWER 42 OF 42 REGISTRY COPYRIGHT 2000 ACS
RN **127779-20-8** REGISTRY
CN Butanediamide, N1-[(1S,2R)-3-[(3S,4aS,8aS)-3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-, (2S)- (9CI) (CA

INDEX NAME)
OTHER CA INDEX NAMES:
CN Butanediamide, N1-[3-[3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-, [3S-[2[1R*(R*),2S*],3.alpha.,4a.beta.,8a.beta.]]-
OTHER NAMES:
CN (S)-N-[(.alpha.S)-.alpha.-[(1R)-2-[(3S,4aS,8aS)-3-(tert-Butylcarbamoyl)octahydro-2(1H)-isoquinolyl]-1-hydroxyethyl]phenethyl]-2-quinaldamidosuccinamide
CN Fortovase
CN Ro 31-8959
CN Ro 31-8959/000
CN Saquinavir
CN Sch 52852
FS STEREOSEARCH
DR 131176-13-1
MF C38 H50 N6 O5
CI COM
SR CA
LC STN Files: ADISINSIGHT, AIDSLINE, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CIN, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IMSDIRECTORY, IPA, MEDLINE, MRCK*, PHAR, PROMT, TOXLINE, TOXLIT, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry.



491 REFERENCES IN FILE CA (1967 TO DATE)
7 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
495 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:275801

REFERENCE 2: 133:261126

REFERENCE 3: 133:256870

REFERENCE 4: 133:247279

REFERENCE 5: 133:246744

REFERENCE 6: 133:232870

REFERENCE 7: 133:232803

REFERENCE 8: 133:232403

REFERENCE 9: 133:232402

REFERENCE 10: 133:232401

=> file caplus

FILE 'CAPLUS' ENTERED AT 12:10:06 ON 06 NOV 2000
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1967 - 6 Nov 2000 VOL 133 ISS 20
FILE LAST UPDATED: 5 Nov 2000 (20001105/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

Now you can extend your author, patent assignee, patent information, and title searches back to 1907. The records from 1907-1966 now have this searchable data in CAOLD. You now have electronic access to all of CA: 1907 to 1966 in CAOLD and 1967 to the present in CAPLUS on STN.

=> d stat que l35 nos

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L7		STR
L11		STR
L15		STR
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L23	390	SEA FILE=REGISTRY SUB=L20 SSS FUL L7
L24	32	SEA FILE=REGISTRY SUB=L20 SSS FUL L11
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L27	12	SEA FILE=CAPLUS ABB=ON PLU=ON L21
L28	34	SEA FILE=CAPLUS ABB=ON PLU=ON L22
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=> d ibib abs hitrn l35 tot

L35 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:414235 CAPLUS
DOCUMENT NUMBER: 129:172230
TITLE: Antibody catalysis of peptidyl-prolyl cis-trans isomerization in the folding of RNase T1
AUTHOR(S): Ma, Lifu; Hsieh-Wilson, Linda C.; Schultz, Peter G.
CORPORATE SOURCE: Howard Hughes Medical Institute, Department of Chemistry, University of California, Berkeley, CA, 94720, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1998), 95(13), 7251-7256
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An antibody generated to an .alpha.-keto amide contg. hapten catalyzes the cis-trans isomerization of peptidyl-prolyl amide bonds in peptides and in the protein RNase T1. The antibody-catalyzed peptide isomerization reaction showed satn. kinetics for the cis-substrate, Suc-Ala-Ala-Pro-Phe-pNA, with a kcat/Km value of 883 s-1.cntdot.M-1; the reaction was inhibited by a hapten analog (Ki = 3.0 .+-. 0.4 .mu.M). Refolding of denatured RNase T1 to its native conformation also was catalyzed by the antibody, with the antibody-catalyzed folding reaction inhibitable both by the hapten and hapten analog. These results demonstrate that antibodies can catalyze conformational changes in protein structure, a transformation involved in many cellular processes.

IT **211385-92-1**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hapten epitope; prepn. of a hapten that elicits an antibody capable of catalyzing peptidyl-prolyl cis-trans isomerization in the folding of RNase T1)

IT **211385-85-2P**
RL: BAC (Biological activity or effector, except adverse); BUU (Biological use, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hapten; prepn. of a hapten that elicits an antibody capable of catalyzing peptidyl-prolyl cis-trans isomerization in the folding of RNase T1)

IT **211385-93-2P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of a hapten that elicits an antibody capable of catalyzing peptidyl-prolyl cis-trans isomerization in the folding of RNase T1)

L35 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:494358 CAPLUS
DOCUMENT NUMBER: 127:187448
TITLE: Catalytic antibodies with PPIase activity
AUTHOR(S): Yli-Kauhaluoma, Jari
CORPORATE SOURCE: Technical Research Centre of Finland, VTT, Chemical Technology, Catalytic Synthesis Technology, Espoo, FIN-02150, Finland
SOURCE: Acta Polytech. Scand., Chem. Technol. Ser. (1997), 247, 92-97
CODEN: APSCF4; ISSN: 1239-0518
PUBLISHER: Finnish Academy of Technology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors report here the design of appropriate hapten to program and study antibody active-sites that model a subset of features used by enzymes.

IT **194288-98-7**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(catalytic antibodies with PPIase activity)

IT **194289-04-8P 194289-05-9P 194289-06-0P**
194289-07-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(catalytic antibodies with PPIase activity)

L35 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:473732 CAPLUS
DOCUMENT NUMBER: 127:81793
TITLE: Preparation of hydroxyethylamine core structures as HIV and FIV protease inhibitors
INVENTOR(S): Wong, Chi-Huey; Slee, Deborah H.; Laslo, Karen
PATENT ASSIGNEE(S): Scripps Research Institute, USA; Wong, Chi-Huey; Slee, Deborah H.; Laslo, Karen
SOURCE: PCT Int. Appl., 202 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9721100	A1	19970612	WO 1996-US19571	19961209
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2238337	AA	19970612	CA 1996-2238337	19961209
AU 9712844	A1	19970627	AU 1997-12844	19961209
EP 873519	A1	19981028	EP 1996-943657	19961209
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2000502332	T2	20000229	JP 1997-521485	19961209
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			WO 1996-US19571	19961209

OTHER SOURCE(S): MARPAT 127:81793
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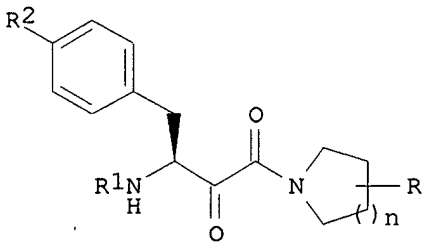

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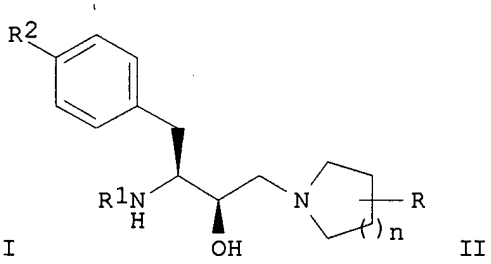

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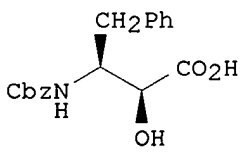

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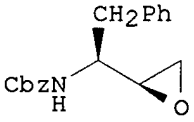


IV

Searched by Edward Hart 305-9203

AB Combinatorial libraries of HIV and FIV protease inhibitors are characterized by .alpha.-keto amide or hydroxyethylamine core structures I and II [n = 1, 2; R = one or more groups CONHCMe3, CH2OH, CH2OMe, CH2OCH2Ph, OH, OCH2Ph, C1-4 alkoxy, optionally nitro-substituted 2-, 3-, or 4-MeOC6H4CH2O, 2,3- or 3,4-methylenedioxyphenylmethoxy, etc.; R1 = PhCH2O2C (Cbz), Me3CO2C (Boc), acyl; R2 = H, HO, PhCH2O, C1-4 alkoxy, optionally nitro-substituted 2-, 3-, or 4-MeOC6H4CH2O, 2,3- or 3,4-methylenedioxyphenylmethoxy] flanked by on one side by substituted pyrrolidines, piperidines, or azasugars and on the other side by Phe, Tyr, or substituted tyrosines. The libraries are synthesized via coupling of the nitrogen heterocycles with hydroxy acids, e.g. III, followed by oxidn. to the keto amide, or a one-step coupling with epoxides, e.g. IV. Highly efficacious drug candidates are identified by screening the libraries for binding and inhibitory activity against both HIV and FIV protease. Drug candidates displaying clin. useful activity against both HIV and FIV protease are identified as being potentially resistive against a loss of inhibitory activity due to development of resistant strains of HIV.

IT **191849-89-5P 191850-27-8P 191850-28-9P**
191850-29-0P 191850-30-3P 191850-31-4P
191850-32-5P 191850-33-6P 191850-34-7P
191850-35-8P 191850-36-9P 191850-37-0P
191850-38-1P 191850-59-6P 191850-60-9P
191850-61-0P 191850-91-6P 191850-92-7P
191850-93-8P 191850-94-9P 191850-95-0P
191850-96-1P 191851-37-3P 191851-38-4P
191851-39-5P 191851-40-8P 191851-42-0P
191851-43-1P 191873-63-9P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of hydroxyethylamine core structures as HIV and FIV protease inhibitors)

IT **191851-51-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of hydroxyethylamine core structures as HIV and FIV protease inhibitors)

L35 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:315749 CAPLUS
DOCUMENT NUMBER: 125:28759
TITLE: Catalytic Antibodies with Peptidyl-Prolyl Cis-Trans Isomerase Activity
AUTHOR(S): Yli-Kauhaluoma, Jari T.; Ashley, Jon A.; Lo, Chih-Hung L.; Coakley, Julie; Wirsching, Peter; Janda, Kim D.
CORPORATE SOURCE: Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: J. Am. Chem. Soc. (1996), 118(23), 5496-5497
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mechanism of the immunophilin peptidyl-prolyl isomerases has not been completely established. The work of others led to the hypothesis that the dicarbonyl moiety in peptide-like immunophilin ligands was a twisted-amide mimetic. To examine the possible influence of this functionality in catalysis, a tripeptide analog contg. an .alpha.-ketoamide bond to the nitrogen of proline was used as a hapten to elicit antibodies having rotamase activity. A panel of 28 monoclonal antibodies (mAbs) was obtained of which 2 increased the rate of P1-prolyl cis to trans isomerization of tripeptide substrates. The mAbs operated with high substrate specificity and gave rate enhancements up to 27-fold over the spontaneous interconversion. In light of the hydrophobic nature of the peptides and data from kinetic and binding studies, it was concluded that the programming of the antibody site by the .alpha.-ketoamide hapten afforded both desolvation effects and geometric constraints that played a

role in catalysis.

IT **177654-10-3**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(catalytic antibodies with peptidyl-prolyl cis-trans isomerase activity)

IT **177654-09-0**
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(catalytic antibodies with peptidyl-prolyl cis-trans isomerase activity)

L35 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:938815 CAPLUS
DOCUMENT NUMBER: 124:105570
TITLE: Selectivity in the Inhibition of HIV and FIV Protease: Inhibitory and Mechanistic Studies of Pyrrolidine-Containing .alpha.-Keto Amide and Hydroxyethylamine Core Structures
AUTHOR(S): Slee, Deborah H.; Laslo, Karen L.; Elder, John H.; Ollmann, Ian R.; Gustchina, Alla; Kervinen, Jukka; Zdanov, Alexander; Wlodawer, Alexander; Wong, Chi-Huey
CORPORATE SOURCE: Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: J. Am. Chem. Soc. (1995), 117(48), 11867-78
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study describes the development of new pyrrolidine-contg. .alpha.-keto amide and hydroxyethylamine core structures as mechanism based inhibitors of the HIV and FIV proteases. The .alpha.-keto amide core structure is approx. 300-fold better than the corresponding hydroxyethylamine isosteric structure and 1300-fold better than the corresponding phosphinic acid deriv. as an inhibitor of the HIV protease. The .alpha.-keto amide is however not hydrated until it is bound to the HIV protease as indicated by the NMR study and the x-ray structural anal. Further anal. of the inhibition activities of hydroxyethylamine isosteres contg. modified pyrrolidine derivs. revealed that a cis-methoxy group at C-4 of the pyrrolidine would improve the binding 5- and 25-fold for the trans-isomer. Of the core structures prepd. as inhibitors of the HIV protease, none show significant inhibitory activity against the mechanistically identical FIV protease, and addnl. complementary groups are needed to improve inhibition.

IT **141197-75-3P**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(HIV and FIV proteases inhibition by pyrrolidine-contg. .alpha.-keto amide and hydroxyethylamines)

IT **172696-14-9P 172883-15-7P 172953-21-8P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(HIV and FIV proteases inhibition by pyrrolidine-contg. .alpha.-keto amide and hydroxyethylamines)

IT **172696-33-2P 172696-34-3P 172823-22-2P**
172823-23-3P 172823-24-4P 172823-25-5P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(reaction with benzyloxycarbonyl chloride)

L35 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:440143 CAPLUS
DOCUMENT NUMBER: 123:112687
TITLE: Synthesis and human immunodeficiency virus (HIV)-1

protease inhibitory activity of tripeptide analogs containing a dioxoethylene moiety

AUTHOR(S): Kitazaki, Tomoyuki; Asano, Tsuneo; Kato, Koichi; Kishimoto, Shoji; Itoh, Katsumi

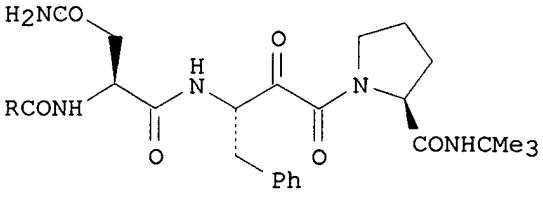
CORPORATE SOURCE: Pharmaceutical Research Laboratories III, Takeda Chemical Industries, Ltd., Osaka, 532, Japan

SOURCE: Chem. Pharm. Bull. (1994), 42(12), 2636-40
CODEN: CPBTAL; ISSN: 0009-2363

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



I

AB Tripeptide analogs I (R = PhCH2O, 2-quinolyl), contg. a dioxoethylene moiety, were designed based on the characteristic structure of the naturally occurring human immunodeficiency virus (HIV)-1 protease inhibitors RPI-856 A, B, C and D. I showed high inhibitory activity, comparable to that of RPI-856 A, against HIV-1 protease in vitro.

IT **141171-73-5P 152843-00-0P 165522-25-8P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and human immunodeficiency virus-1 protease inhibitory activity of tripeptide analogs contg. a dioxoethylene moiety)

L35 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1994:289408 CAPLUS

DOCUMENT NUMBER: 120:289408

TITLE: Three-dimensional QSAR of human immunodeficiency virus (I) protease inhibitors. 1. A CoMFA study employing experimentally-determined alignment rules

AUTHOR(S): Waller, Chris L.; Oprea, Tudor I.; Giolitti, Alessandro; Marshall, Garland R.

CORPORATE SOURCE: Cent. Mol. Des., Washington Univ., St. Louis, MO, 63130, USA

SOURCE: J. Med. Chem. (1993), 36(26), 4152-60
CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Comparative mol. field anal. (CoMFA), a 3-dimensional, quant. structure-activity relationship (QSAR) paradigm, was used to exam. the correlations between the calcd. physicochem. properties and in the vitro activities of a series of human immunodeficiency virus (HIV-1) protease inhibitors. The training set consisted of 59 mols. from five structurally-diverse transition-state isostere classes: hydroxyethylamine, statine, norstatine, keto amide, and dihydroxyethylene. The availability of x-ray crystallog. data for at least one representative from each class bound to the protease provided information regarding not only the active conformation of each ligand but also, via superimposition of protease backbones, the relative positions of each ligand with respect to one another in the active site of the enzyme. Once aligned, these mols. served as templates on which addnl. congeners were field-fit minimized. Addnl. alignment rules were derived from minimization of the ligands in

the active site of the semirigid protease. The predictive ability of each resultant model was evaluated using a test set comprised of mols. contg. a novel transition-state isostere: hydroxyethylurea. Crystallog. studies indicated an unexpected binding mode for this series of compds. which precluded the use of the field-fit minimization alignment technique. The test set mols. were, therefore, subjected to a limited systematic search in conjunction with active-site minimization. The conformer of each mol. expressing the lowest interaction energy with the active site was included in the test set. Field-fit minimization of neutral mols. to crystal ligands and active-site minimizations of protonated ligands yielded predictive correlations for HIV-1 protease inhibitors. The use of crystallog. data in the detn. of alignment rules and field-fit minimization as a mol. alignment tool in the absence of direct exptl. data regarding binding modes is strongly supported by these results.

IT **141171-73-5 141197-75-3**
RL: BIOL (Biological study)
(human immunodeficiency virus 1 protease inhibition by, QSAR of)

L35 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:245780 CAPLUS
DOCUMENT NUMBER: 120:245780
TITLE: Preparation of asparagine-containing peptide derivatives as retrovirus protease inhibitors
INVENTOR(S): Ito, Katsumi; Kato, Koichi
PATENT ASSIGNEE(S): Takeda Chemical Industries Ltd, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 14 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 05178824	A2	19930720	JP 1992-159678	19920618
PRIORITY APPLN. INFO.:			JP 1991-195469	19910805

OTHER SOURCE(S): MARPAT 120:245780
GI For diagram(s), see printed CA Issue.
AB The title compds. (I; ring A = 5- to 6-membered ring; R1 = R2 = H or R1R2 forms a fused ring; R3 = optionally esterified or amidated CO2H; R4 = H, acyl; X = CHOH, CO), useful for the treatment of diseases caused by retroviruses, e.g. human immunodeficiency virus (HIV) causing AIDS, adult T-cell leukemia virus (ATLV), human T-cell leukemia virus type I (HTLV-I), and T-cell hairycell leukemia, are prepd. Thus, H-Pro-NHCMe3 was condensed with (2RS,3S)-3-benzyloxycarbonylamino-2-hydroxy-4-phenylbutanoic acid in the presence of (EtO)2P(O)CN and Et3N in DMF to give N.alpha.-[(3S)-3-benzyloxycarbonylamino-2-hydroxy-4-phenylbutyryl]-N-tert-butyl-L-prolinamide as a diastereomeric mixt., which (more polar diastereomer) was hydrogenolyzed over 10% Pd-C in aq. MeOH to give N.alpha.-[(3S)-3-amino-2-hydroxy-4-phenylbutyryl]-N-tert-butyl-L-prolinamide. The latter was condensed with Boc-Asn-C6H4NO2-p in DMF to give N.alpha.-[(3S)-3-(N.alpha.-benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutyryl]-N-tert-butyl-L-prolinamide, which showed IC50 of 0.020 .mu.M against recombinant HIV-1 protease. Addnl. 3 were prepd.

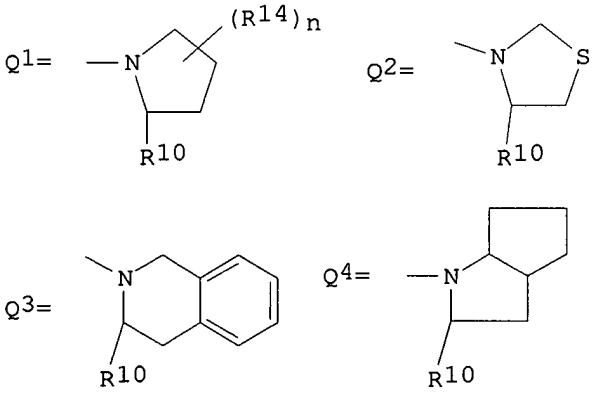
IT **141171-73-5P 152843-00-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as retrovirus protease inhibitor)

L35 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:245776 CAPLUS
DOCUMENT NUMBER: 120:245776
TITLE: Preparation of cyclic amides of 3-amino-2-hydroxycarboxylic acids as HIV protease inhibitors
INVENTOR(S): Krantz, Alexander; Tam, Tim Fat; Castelhano, Arlindo

Lucas; Nestor, John Joseph, Jr.
PATENT ASSIGNEE(S): Syntex (U.S.A.), Inc., USA
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9313066	A1	19930708	WO 1992-US10772	19921218
W: AU, CA, FI, HU, JP, KR, NO, NZ				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9332782	A1	19930728	AU 1993-32782	19921218
ZA 9209869	A	19940620	ZA 1992-9869	19921218
PRIORITY APPLN. INFO.:			US 1991-812905	19911220
			WO 1992-US10772	19921218

OTHER SOURCE(S): MARPAT 120:245776
GI



AB R1R2NCHR3CONHCHR4CR5R6COR7 [R1 = (ar)alkoxycarbonyl, (substituted) aralkanoyl, aroyl, heterocyclylcarbonyl, aryloxyalkanoyl, carbamoyl, heterocyclyloxyalkanoyl; R2, R5 = H; R3 = (substituted) alkyl, R4 = (substituted) aryl, aralkyl; R6 = OH; R5R6 = O; R1 = Q1-Q4, etc.; n = 0-2; R10 = alkoxycarbonyl, (substituted) carbamoyl; R14 = OH, alkyl, alkoxy, Ph], were prepd. Thus, N'-tert-Bu prolinamide (prepn. given) was coupled with (2S,3S)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoic acid using EDCI/hydroxybenzotriazole in DMF to give 1-[(2S,3S)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-N'-tert-butyl-L-prolinamide. I inhibited HIV protease with IC50 = 0.49-30 nM. I dosage formulations are given.
IT **141171-73-5P 141197-75-3P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of, as HIV protease inhibitor)

L35 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1992:227702 CAPLUS
DOCUMENT NUMBER: 116:227702
TITLE: Intriguing structure-activity relations underlie the potent inhibition of HIV protease by norstatine-based peptides
AUTHOR(S): Tam, Tim F.; Carriere, Julie; MacDonald, I. David;
Searched by Edward Hart 305-9203

Castelhano, Arlindo L.; Pliura, Diana H.; Dewdney, Nolan J.; Thomas, Everton M.; Bach, Chinh; Barnett, Jimmy; et al.
CORPORATE SOURCE: Syntex Res. Canada, Mississauga, ON, L5N 3X4, Can.
SOURCE: J. Med. Chem. (1992), 35(7), 1318-20
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Phenylnorstatine contg. peptides extending from the P2 to P1' positions, with L-proline at the P1' position and S-stereochem. of the P1 component, exhibit impressive potency vs. HIV-1 potease (IC50 = 0.58-7.4 nM). Representative ketoamides are also active with slightly lower potency. Analogous hydroxyethylamines have previously been reported to be potent inhibitors of this enzyme. The presence of an addnl. carbonyl in this series of proline-based inhibitors enhances their potency, and alters structure-activity relations profoundly. Whereas divergent effects on potency have been obsd. for epimeric hydroxyethylamines upon extension of such P1' terminal peptides to P3' with Ile-Val, lengthening of norstatine contg.-inhibitors in the same fashion, dramatically increases the potency of the R-diastereomer and leaves the IC50 of the S-epimer essentially unchanged. Most interestingly, amino acid residues in the P1' position contg. parent and fused piperidines lower activity in the norstatine series. By contrast, significant enhancements in inhibitor potency were reported in the hydroxyethylamine series for such proline replacements. Conformational preferences of 6 member rings influenced by A1,3-strain may contribute to the redn. in potency obsd. for the norstatine contg. peptides.

IT **141171-73-5 141197-75-3**
RL: BIOL (Biological study)
(human immunodeficiency virus 1 protease inhibition by)

=> file reg

FILE 'REGISTRY' ENTERED AT 12:11:34 ON 06 NOV 2000
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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STRUCTURE FILE UPDATES: 5 NOV 2000 HIGHEST RN 301296-06-0
DICTIONARY FILE UPDATES: 5 NOV 2000 HIGHEST RN 301296-06-0

TSCA INFORMATION NOW CURRENT THROUGH July 8, 2000

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Structure search limits have been increased. See HELP SLIMIT for details.

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YOU HAVE REQUESTED DATA FROM FILE 'CAPLUS' - CONTINUE? (Y)/N:n

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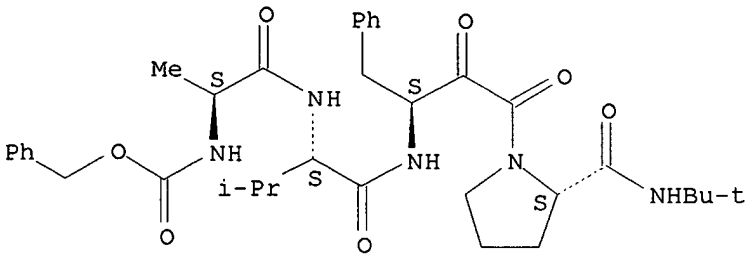
L21 ANSWER 1 OF 55 REGISTRY COPYRIGHT 2000 ACS
RN 227317-37-5 REGISTRY
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-L-alanyl-L-valyl-(.beta.S)-.beta.-amino-.alpha.-oxobenzenebutanoyl-N-(1,1-dimethylethyl)- (9CI) (CA INDEX NAME)

FS PROTEIN SEQUENCE; STEREOSEARCH
MF C35 H47 N5 O7
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

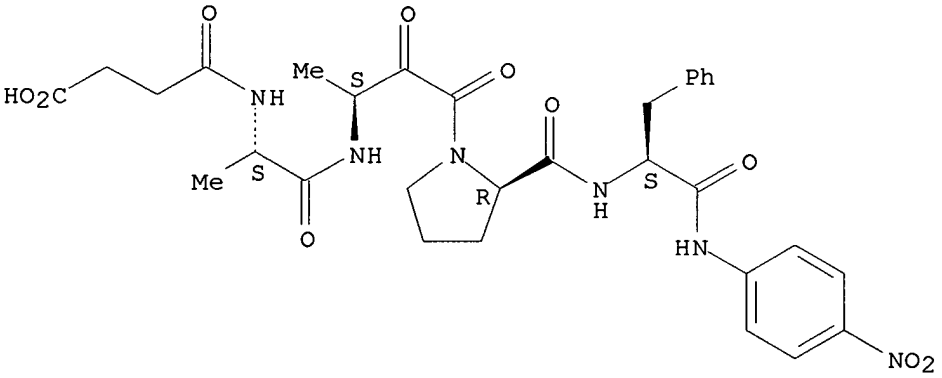


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

L21 ANSWER 5 OF 55 REGISTRY COPYRIGHT 2000 ACS
RN 211385-85-2 REGISTRY
CN L-Phenylalaninamide, N-(3-carboxy-1-oxopropyl)-L-alanyl-(3S)-3-amino-2-oxobutanoyl-D-prolyl-N-(4-nitrophenyl)- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C31 H36 N6 O10
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

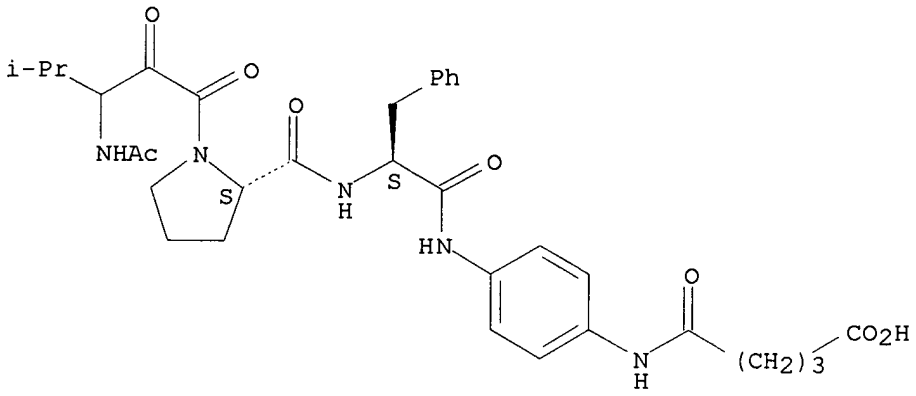


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:172230

L21 ANSWER 10 OF 55 REGISTRY COPYRIGHT 2000 ACS
RN 194288-98-7 REGISTRY
CN L-Phenylalaninamide, 1-[3-(acetylamino)-4-methyl-1,2-dioxopentyl]-L-prolyl-N-[4-[(4-carboxy-1-oxobutyl)amino]phenyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C33 H41 N5 O8
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

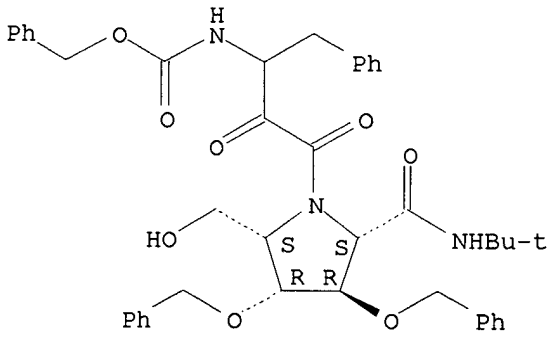


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:187448

L21 ANSWER 15 OF 55 REGISTRY COPYRIGHT 2000 ACS
RN 191851-40-8 REGISTRY
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-5-(hydroxymethyl)-3,4-bis(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.,4.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C42 H47 N3 O8
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

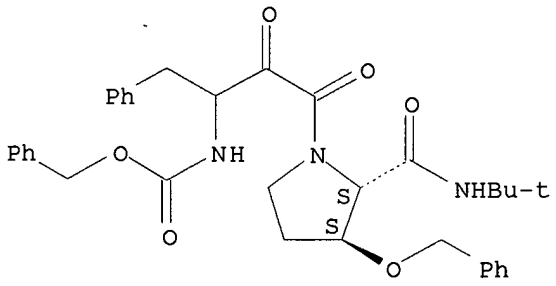


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:81793

L21 ANSWER 20 OF 55 REGISTRY COPYRIGHT 2000 ACS
RN 191850-95-0 REGISTRY
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.)]-[partial]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C34 H39 N3 O6
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

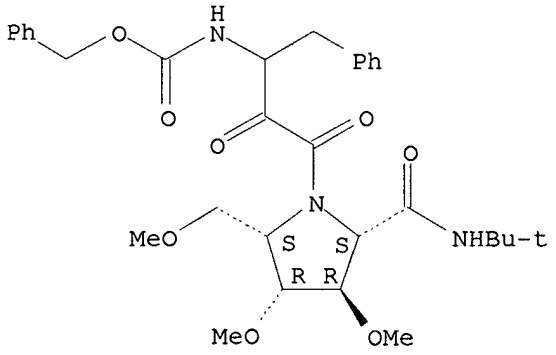


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:81793

L21 ANSWER 25 OF 55 REGISTRY COPYRIGHT 2000 ACS
RN 191850-61-0 REGISTRY
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3,4-dimethoxy-5-(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.,4.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C31 H41 N3 O8
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

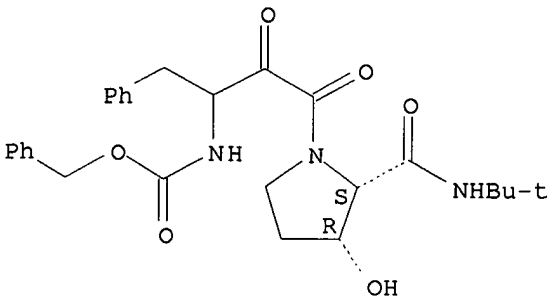


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:81793

L21 ANSWER 30 OF 55 REGISTRY COPYRIGHT 2000 ACS
RN 191850-36-9 REGISTRY
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3-hydroxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.alpha.)]-[partial]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H33 N3 O6
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

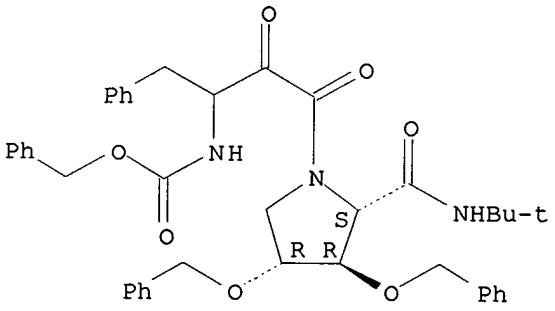


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:81793

L21 ANSWER 35 OF 55 REGISTRY COPYRIGHT 2000 ACS
RN 191850-31-4 REGISTRY
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3,4-bis(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.,4.alpha.)]-[partial]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C41 H45 N3 O7
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

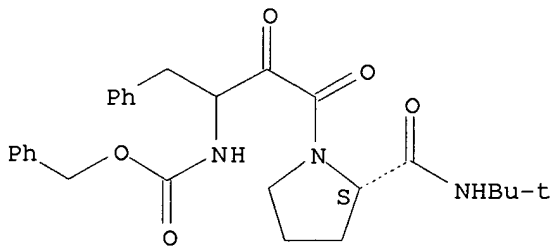


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:81793

L21 ANSWER 40 OF 55 REGISTRY COPYRIGHT 2000 ACS
RN 191849-89-5 REGISTRY
CN Carbamic acid, [3-[(2S)-2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, (2S)-
FS STEREOSEARCH
MF C27 H33 N3 O5
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



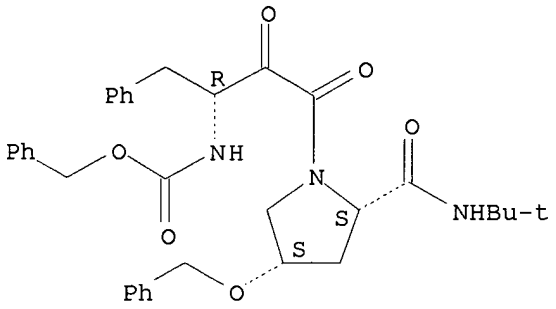
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:276229

REFERENCE 2: 127:81793

L21 ANSWER 45 OF 55 REGISTRY COPYRIGHT 2000 ACS
RN 172823-25-5 REGISTRY
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-[1(S*),2.alpha.,4.alpha.]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C34 H39 N3 O6
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.

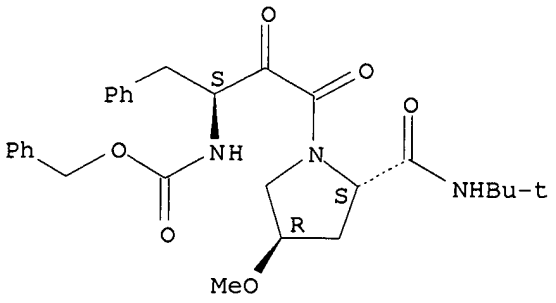


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:105570

L21 ANSWER 50 OF 55 REGISTRY COPYRIGHT 2000 ACS
RN 172696-33-2 REGISTRY
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-[1(R*),2.alpha.,4.beta.]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C28 H35 N3 O6
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.

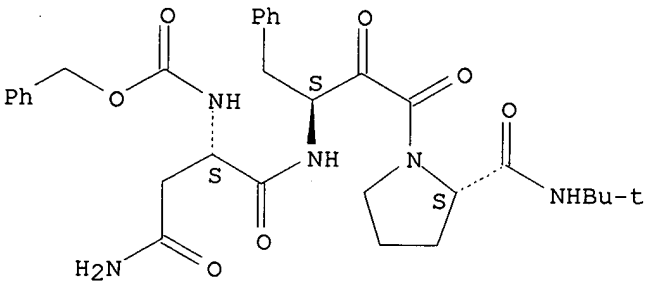


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:105570

L21 ANSWER 55 OF 55 REGISTRY COPYRIGHT 2000 ACS
RN 141171-73-5 REGISTRY
CN Carbamic acid, [3-amino-1-[[[3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]amino]carbonyl]-3-oxopropyl]-, phenylmethyl ester, [2S-[1[R*(R*)],2R*]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C31 H39 N5 O7
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, TOXLIT
(*File contains numerically searchable property data)

Absolute stereochemistry.



5 REFERENCES IN FILE CA (1967 TO DATE)
5 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 123:112687

REFERENCE 2: 120:289408

REFERENCE 3: 120:245780

REFERENCE 4: 120:245776

REFERENCE 5: 116:227702

=> file caplus

FILE 'CAPLUS' ENTERED AT 12:12:59 ON 06 NOV 2000
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
Searched by Edward Hart 305-9203

FILE COVERS 1967 - 6 Nov 2000 VOL 133 ISS 20
FILE LAST UPDATED: 5 Nov 2000 (20001105/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

Now you can extend your author, patent assignee, patent information, and title searches back to 1907. The records from 1907-1966 now have this searchable data in CAOLD. You now have electronic access to all of CA: 1907 to 1966 in CAOLD and 1967 to the present in CAPLUS on STN.

=> d stat que 137 nos

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L1              STR
L5              STR
L7              STR
L11             STR
L15             STR
L17             STR
L20        1079 SEA FILE=REGISTRY SSS FUL L1 OR L5 OR L7 OR L11 OR L15 OR L17
L21          55 SEA FILE=REGISTRY SUB=L20 SSS FUL L1
L22         370 SEA FILE=REGISTRY SUB=L20 SSS FUL L5
L23         390 SEA FILE=REGISTRY SUB=L20 SSS FUL L7
L24          32 SEA FILE=REGISTRY SUB=L20 SSS FUL L11
L25         168 SEA FILE=REGISTRY SUB=L20 SSS FUL L15
L26          93 SEA FILE=REGISTRY SUB=L20 SSS FUL L17
L27          12 SEA FILE=CAPLUS ABB=ON  PLU=ON  L21
L28          34 SEA FILE=CAPLUS ABB=ON  PLU=ON  L22
L29         100 SEA FILE=CAPLUS ABB=ON  PLU=ON  L23
L30          11 SEA FILE=CAPLUS ABB=ON  PLU=ON  L24
L31         527 SEA FILE=CAPLUS ABB=ON  PLU=ON  L25
L32         439 SEA FILE=CAPLUS ABB=ON  PLU=ON  L26
L33           2 SEA FILE=CAPLUS ABB=ON  PLU=ON  L27 AND L28 AND L29 AND L30
                AND L31 AND L32
L36          26 SEA FILE=CAPLUS ABB=ON  PLU=ON  L28 NOT (L33 OR L27)
L37          19 SEA FILE=CAPLUS ABB=ON  PLU=ON  L36 NOT (2000 OR 1999 OR
                1998)/PY
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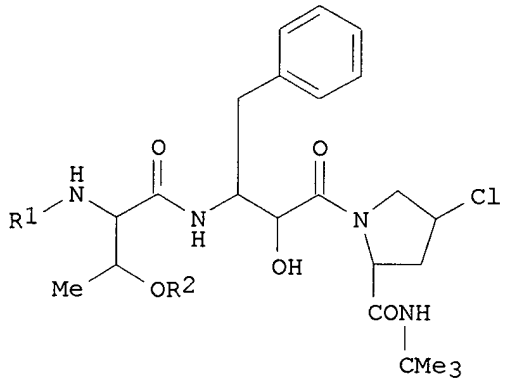
=> d ibib abs hitrn 137 tot

L37 ANSWER 1 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:8618 CAPLUS
DOCUMENT NUMBER: 128:149570
TITLE: AHPBA-containing tripeptides and their uses as anti-AIDS drugs and HIV protease inhibitors
INVENTOR(S): Yabe, Yuichiro; Watanabe, Takashi; Nishigaki, Takashi; Ozawa, Yuji; Komai, Tomoaki; Nakagawa, Akihiko
PATENT ASSIGNEE(S): Sankyo Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 20 pp.
CODEN: JKXXAF
Searched by Edward Hart 305-9203

DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 09328428	A2	19971222	JP 1996-145480	19960607

GI



I

AB Therapeutic and prophylactic agents for AIDS and HIV protease inhibitors contain the tripeptides I [R1 = quinoline-2-carbonyl, quinoxaline-2-carbonyl; R2 = H, C1-4 alkyl, Ac, CH2OMe, CH2OAc, CH2OCOCMe3, CO(CH2)nCO2H (n = 2-4), COCH2OCH2CO2H] or their salts and pharmacol. acceptable carriers or excipients. I inhibited HIV protease and suppressed release of HIV (HTLV IIIB) from CEM cells. Pharmaceutical formulations of 2(S),3(S)-3-[N-(quinoxaline-2-carbonyl)-L-threonyl]amino-2-hydroxy-4-phenylbutanoyl-[4(S)-chloro]-L-proline tert-butylamide (prepn. given) were also given.

IT **180266-04-0P 180266-05-1P 180266-06-2P**
180266-07-3P 180266-08-4P 180266-09-5P
180266-10-8P 180266-11-9P 180467-99-6P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of AHPBA-contg. tripeptides as HIV protease inhibitors and anti-AIDS drugs contg. them)

IT **180468-02-4**
RL: RCT (Reactant)
(prepn. of AHPBA-contg. tripeptides as HIV protease inhibitors and anti-AIDS drugs contg. them)

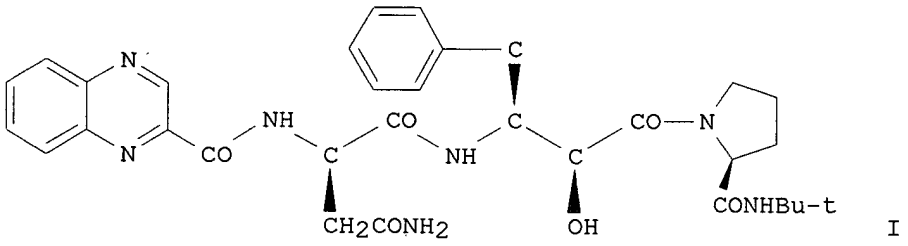
IT **180266-12-0P 180266-18-6P 180266-20-0P**
180468-00-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of AHPBA-contg. tripeptides as HIV protease inhibitors and anti-AIDS drugs contg. them)

L37 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:555386 CAPLUS
DOCUMENT NUMBER: 127:195514
TITLE: Percutaneous formulations
INVENTOR(S): Inoue, Kazuhiro; Ogawa, Kengo; Suzuki, Yukie; Okada, Junichi
PATENT ASSIGNEE(S): Sankyo Co., Ltd., Japan
Searched by Edward Hart 305-9203

SOURCE: Jpn. Kokai Tokkyo Koho, 46 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 09194355	A2	19970729	JP 1996-298455	19961111
PRIORITY APPLN. INFO.:			JP 1995-293896	19951113

OTHER SOURCE(S): MARPAT 127:195514
GI



I

AB Compns. showing excellent percutaneous absorption contain polycyclic compds. such as I and decanoyl-N-methylglucamide and/or undecanoyl-N-methylglucamide. I 1 and decanoyl-N-methylglucamide 10 g were mixed and dissolved in 200 mL pH 7 phosphate buffer (2 M) with stirring overnight to give a soln. for skin application. In vitro expts. indicated that the formulations showed high permeability to isolated mouse skin.

IT **194412-24-3 194412-25-4 194412-26-5 194412-28-7**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(percutaneous dosage forms)

L37 ANSWER 3 OF 19 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1997:137427 CAPLUS
DOCUMENT NUMBER: 126:246375
TITLE: In vitro and ex vivo anti-human immunodeficiency virus (HIV) activities of a new water-soluble HIV protease inhibitor, R-87366, containing (2S,3S)-3-amino-2-hydroxy-4-phenylbutanoic acid
AUTHOR(S): Komai, Tomoaki; Yagi, Ryuichi; Suzuki-Sunagawa, Hisayo; Sakurai, Mitsuya; Higashida, Susumu; Sugano, Machiko; Handa, Hiroshi; Mohri, Hiroshi; Yasuoka, Akira; et al.
CORPORATE SOURCE: Biological Research Laboratories, Sankyo Co., Ltd., Tokyo, 140, Japan
SOURCE: Biol. Pharm. Bull. (1997), 20(2), 175-180
CODEN: BPBLEO; ISSN: 0918-6158
PUBLISHER: Pharmaceutical Society of Japan
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In a series of compds. contg. (2S,3S)-3-amino-2-hydroxy-4-phenylbutanoic acid (AHPBA), a transition-state mimetic, R-87366:(2S,3S)-3-[N-(quinoxaline-2-carbonyl)-L-asparaginyl]amino-2-hydroxy-4-phenylbutanoyl-L-proline-tert-butylamide, was a potent human immunodeficiency virus protease inhibitor (Ki value was 11 nM) and anti-HIV agent (IC90 value was 0.5 .mu.M for HIV-1IIIB acutely infected cells) with moderate water-soly. (4.2 mg/mL at 25.degree.). The compd. was also active in chronically

infected Molt-4/HIV-1IIIB cells, and inhibited the proteolytic processing of p55 into p17, suggesting that its anti-HIV activity was derived from HIV protease inhibition. The compd. showed more potent activity (IC90 value was 0.03-0.25 .mu.M) against clin. isolates of HIV in 5 out of 6 patients examd. with varying clin. status in an ex vivo assay. One isolate, however, from the sixth patient, was less sensitive to R-87366 (IC90 value was 0.5 .mu.M). In expts. with this strain, R-87366 showed comparatively low efficacy in acutely infected peripheral blood mononuclear cell (PBMC). This result suggests that the diversity of sensitivity shown in the ex vivo assay could be caused by the viral property itself. As a result of the detn. of nucleic acid sequences in the clin. isolates, some amino acids were substituted in the protease region, in contrast to the HIV-1 clade B consensus sequence, and some of them have been reported to contribute to the susceptibility of HIV protease inhibitors.

IT **139694-65-8 141171-80-4 144779-91-9**, R 87366
144780-41-6
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiviral activity of water-sol. HIV protease inhibitor R-87366 and analogs against HIV-1)

L37 ANSWER 4 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:693923 CAPLUS
DOCUMENT NUMBER: 126:114991
TITLE: Expression, characterization, and mutagenesis of the aspartic proteinase from equine infectious anemia virus
AUTHOR(S): Powell, David J.; Bur, Daniel; Wlodawer, Alexander; Gustchina, Alla; Payne, Susan L.; Dunn, Ben M.; Kay, John
CORPORATE SOURCE: College Cardiff, Univ. Wales, Cardiff, CF1 3US, UK
SOURCE: Eur. J. Biochem. (1996), 241(2), 664-674
CODEN: EJBCAI; ISSN: 0014-2956
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The gene encoding the proteinase from equine infectious anemia virus (EIAV) was cloned and expressed in Escherichia coli. The recombinant EIAV proteinase was purified to homogeneity and shown to have the ability to process polyprotein and synthetic peptide substrates of human immunodeficiency virus (HIV) origin with an efficiency that can approach that exhibited by HIV proteinase. EIAV proteinase, however, was not susceptible to inhibition by a wide variety of inhibitors HIV-1 proteinase, including those which have been licensed as anti-AIDS drugs. In this respect, EIAV proteinase behaves like an extreme case of a drug-resistant mutant of HIV-1 proteinase that has arisen under selective drug pressure. Only one potent inhibitor (HBY-793) of HIV-1 proteinase showed comparable efficiency against the EIAV enzyme; the compds. A-77003 and A-76889, which differ only in their stereochem. and which are otherwise structurally identical to HBY-793 from residues P2 to P2' [nomenclature of Schechter, I. & Berger, A. (1967) Biochem. Biophys. Res. Commun. 27, 157-162], were not effective inhibitors of EIAV proteinase. Mutant forms of EIAV proteinase (Thr30.fwdarw.Asp and Ile54.fwdarw.Gly) were generated and their ability to interact with substrates and inhibitors was characterized. HBY-793 inhibited [Gly54]proteinase as effectively as the wild-type proteinase but was tenfold less potent against [Asp30]proteinase. Data interpretations are presented, based on the structure solved for the complex between HBY-793 and EIAV [Gly54]proteinase [Gustchina A., Kervinen, J., Powell, D. J., Zdanov, A., Kay, J. & Wlodawer, A. (1996) Protein Sci. 5, 1453-1465].

IT **141171-80-4**, RO 32-1636
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)

(substrate specificity, susceptibility to HIV proteinase inhibitors , ability to process HIV gag polyprotein, and mutagenesis of recombinant aspartic proteinase from equine infectious anemia virus)

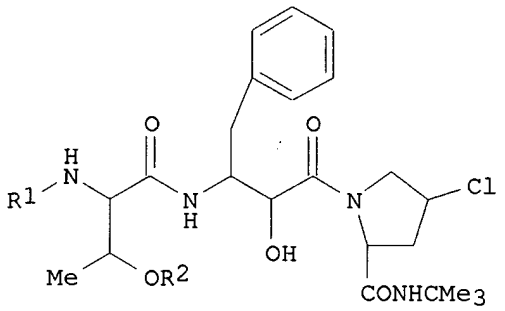
L37 ANSWER 5 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:572390 CAPLUS
DOCUMENT NUMBER: 125:292240
TITLE: Structure-activity relationships of HIV-1 PR inhibitors containing AHPBA-II. Modification of pyrrolidine ring at P1' proline
AUTHOR(S): Komai, Tomoaki; Higashida, Susumu; Sakurai, Mitsuya; Nitta, Tamayo; Kasuya, Atsushi; Miyamaoto, Shuichi; Yagi, Ryuichi; Ozawa, Yuji; Handa, Hiroshi; et al.
CORPORATE SOURCE: Biological Res. Lab., Sankyo Co. Ltd., Tokyo, 140, Japan
SOURCE: Bioorg. Med. Chem. (1996), 4(8), 1365-1377
CODEN: BMECEP; ISSN: 0968-0896
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Systematic replacement in the 3- or 4-position of the pyrrolidine ring at P1' proline was carried out. Compd. 26, which has a Cl atom in the 4(S)-position was the most active among inhibitors substituted with other halogen atoms or other substituents. Furthermore, the replacement of the Z group in compd. 26 with five- or six-membered fused arom. heterocycle carbonyl groups produced more potent inhibitors. 7-Methoxybenzofuran-2-carbonyl deriv. (44) was the best of these and showed Ki = 4.5 nM against HIV PR and IC90s 0.58 .mu.M and 0.06 .mu.M in chronic and acute infections, resp. These results suggest that the combination of the 4(S)-Cl atom and fused bicyclic heterocycles may be effective in improving their cellular penetration.
IT **153290-12-1P 153380-13-3P 166382-65-6P**
166382-66-7P 166382-67-8P 166382-69-0P
166382-72-5P 166382-73-6P 166382-74-7P
166382-96-3P 166383-38-6P 166383-39-7P
166583-08-0P 166583-09-1P
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(structure-activity relationship and prepn. of HIV-1 protease inhibitors contg. amino-hydroxy-phenylbutanoic acid)
IT **166382-75-8P 166383-43-3P 166383-44-4P**
166383-45-5P 166383-46-6P 166383-47-7P
166383-48-8P
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(structure-activity relationship and prepn. of HIV-1 protease inhibitors contg. amino-hydroxy-phenylbutanoic acid)

L37 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:516494 CAPLUS
DOCUMENT NUMBER: 125:168657
TITLE: Preparation of 3-amino-2-hydroxy-4-phenylbutanoic acid-containing tripeptide derivatives as HIV protease inhibitors
INVENTOR(S): Yabe, Yuichiro; Watanabe, Takashi; Nishigaki, Takashi; Ozawa, Yuji; Komai, Tomoaki; Nakagawa, Akihiko
PATENT ASSIGNEE(S): Sankyo Co., Ltd., Japan
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9618627	A1	19960620	WO 1995-JP2546	19951213
W: AU, CA, CN, CZ, FI, HU, KR, MX, NO, NZ, RU, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
JP 08217776	A2	19960827	JP 1995-321385	19951211
AU 9641880	A1	19960703	AU 1996-41880	19951213
PRIORITY APPLN. INFO.:			JP 1994-310419	19941214
			WO 1995-JP2546	19951213

OTHER SOURCE(S): MARPAT 125:168657
GI



I

AB The title compds. [I; R1 = quinoline-2-carbonyl, quinoxaline-2-carbonyl; R2 = H, C1-4 alkyl, Ac, MeSCH2, AcOCH2, pivaloyloxymethyl, HO2C(CH2)nCO, HO2CCH2OCH2CO; n = 2-4], which inhibit HIV protease and release of virus from HIV-infected cells and have excellent absorbability through oral administration, are prepd. Thus, N-[3(S)-amino-2(S)-hydroxy-4-phenylbutanoyl]-4-chloro-L-proline tert-butylamide was dissolved in DMF, treated with Boc-Thr-OH, ice-cooled, treated with di-Et cyanophosphonate and then dropwise with Et3N, and stirred for 3 h to give N-[3(S)-[N-tert-butoxycarbonyl-L-threonylamino]-2(S)-hydroxy-4-phenylbutanoyl]-4-chloro-L-proline tert-butylamide. The latter compd. was treated with 4 N HCl in dioxane to remove the Boc group and then similarly condensed with 2-quinoxalinecarboxylic acid using di-Et cyanophosphorate and Et3N to give N-[3(S)-[N-quinoxaline-2-carbonyl-L-threonylamino]-2(S)-hydroxy-4-phenylbutanoyl]-4-chloro-L-proline tert-butylamide.

IT **180266-04-0P 180266-05-1P 180266-06-2P**
180266-07-3P 180266-08-4P 180266-09-5P
180266-10-8P 180266-11-9P 180467-99-6P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 3-amino-2-hydroxy-4-phenylbutanoic acid-contg. tripeptide derivs. as HIV protease inhibitors)

IT **180266-12-0P 180266-13-1P 180266-18-6P**
180266-19-7P 180266-20-0P 180266-21-1P
180468-00-2P 180468-01-3P 180468-02-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of 3-amino-2-hydroxy-4-phenylbutanoic acid-contg. tripeptide derivs. as HIV protease inhibitors)

L37 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:294964 CAPLUS
DOCUMENT NUMBER: 125:11470
TITLE: Preparation of .beta.-amino-.alpha.-hydroxy carboxylic acids as HIV protease inhibitors
INVENTOR(S): Yabe, Juichiro; Sakurai, Mitsuya; Higashida, Susumu;
Searched by Edward Hart 305-9203

Komai, Tomoaki; Nishigaki, Takashi; Handa, Hiroshi
PATENT ASSIGNEE(S): Sankyo Co, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 11 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 08048627	A2	19960220	JP 1995-222121	19950830

AB (2S,3S)-3-[N-(2-indole- or -quinoxaline-carbonyl)asparaginyl]amino-2-hydroxy-4-phenylbutyrylproline tert-Bu ester, (2S,3S)-3-[N-(5-methoxy-, -hydroxy-, or -acetoxy-indole-2-carbonyl)asparaginyl]amino-2-hydroxy-4-phenylbutyrylproline tert-butylamide, and (2S,3S)-3-[N-(quinoxaline-2-carbonyl)asparaginyl]amino-2-hydroxy-4-phenylbutyrylprolyl-(2-methyl)alaninol are prepd. as HIV infection-preventing or -treating agents or anti-AIDS agents. (2S,3S)-3-asparaginylamino-2-hydroxy-4-phenylbutyrylproline tert-Bu ester HCl salt (60 mg, prepn. given) was treated with 20 mg indole-2-carboxylic acid in DMF in the presence of (EtO)2P(O)CN and NEt3 at 0.degree. for 3 h to give 13 mg (2S,3S)-3-[N-(2-indolecarbonyl)asparaginyl]amino-2-hydroxy-4-phenylbutyrylproline tert-Bu ester, which inhibited HIV pol protease with Ki 25 nM, vs. 58 nM, for Ro 31-8959.

IT **143934-48-9P 177023-66-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(intermediate; prepn. of [(asparaginylamino)butyryl]prolines as HIV protease inhibitors)

IT **139694-65-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(intermediate; prepn. of [(asparaginylamino)butyryl]prolines as HIV protease inhibitors)

IT **144780-25-6P**
RL: BAC (Biological activity or effector, except adverse); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of [(asparaginylamino)butyryl]prolines as HIV protease inhibitors)

IT **144780-24-5P 144780-26-7P 144780-47-2P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of [(asparaginylamino)butyryl]prolines as HIV protease inhibitors)

L37 ANSWER 8 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:128450 CAPLUS
DOCUMENT NUMBER: 124:242317
TITLE: Preparation of anti-AIDS agents containing 3-amino-2-hydroxy-4-butanoic acid derivatives and the oral preparations
INVENTOR(S): Takeuchi, Shohachi; Hiratsuka, Sashichi; Fujisawa, Naoki
PATENT ASSIGNEE(S): Japan Enajii Kk, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

JP 07324032 A2 19951212 JP 1994-139429 19940530
OTHER SOURCE(S): MARPAT 124:242317
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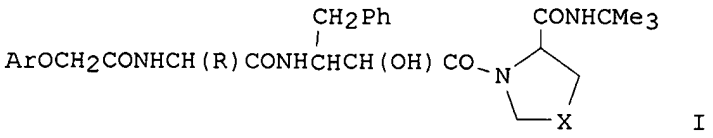

I

AB The anti-AIDS agents are prepd. by coating of solid acidic substances with fine powders of the title derivs. I (Ar = 5-isoquinolinyl, 3-pyridyl; R = CH2SMe, CHMe2; X = S, CH2). Anti-AIDS prepns. contg. the above composite powders are also claimed. The prepns. for oral administration show improved bioavailability. Citric acid powder (av. particle size 7 .mu.m) (200 parts) was mixed with 100 parts powder of (R)-N-tert-butyl-3-[(2S,3S)-2-hydroxy-3-N-[(R)-2-N-(5-isoquinolyloxyacetyl)amino-3-methlthiopropanoyl]amino-4-phenylbutanoyl]1,3-thiazolidine-4-carboxamide (II; av. particle size 2 .mu.m) using a hybridizer to give composite powder. A mixt. of 450 parts composite powder and 2.5 parts light SiO2 was made into granules, which was mixed with excipients and the mixt. was made into enteric-coated tablets contg. 150 mg II/per tablet. The enteric-coated tablet was p.o. administered to beagles to show bioavailability 20.42%, vs. 12.43% for a control tablet prepd. from granules obtained by direct mixing of II 150, citric acid 300, and SiO2 2.5 parts.

IT **174730-46-2**
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(oral AIDS inhibitors prepd. by coating of acidic substance powders with aminohydroxybutanoic acid derivs. for improved bioavailability)

L37 ANSWER 9 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:270980 CAPLUS
DOCUMENT NUMBER: 122:122508
TITLE: Structure-activity relationships of HIV-1 PR inhibitors containing AHPBA
AUTHOR(S): Sakurai, Mitsuya; Higashida, Susumu; Sugano, Machiko; Komai, Tomoaki; Yagi, Ryuichi; Ozawa, Yuji; Handa, Hiroshi; Nishigaki, Takashi; Yabe, Yuichiro
CORPORATE SOURCE: Exploratory Chemistry Research and Biological Research Lab., Sankyo Co. Ltd., Tokyo, 140, Japan
SOURCE: Bioorg. Med. Chem. (1994), 2(8), 807-25
CODEN: BMECEP; ISSN: 0968-0896
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of Human Immunodeficiency Virus type-1 protease (HIV-1 PR) inhibitors that contain 3-amino-2-hydroxy-4-phenylbutanoic acid (AHPBA) at the scission site of the substrate were prepd. and evaluated for their inhibitory activity. Preliminary studies on the chain length of inhibitors and the hydroxyl configuration of AHPBA indicated that small (2S,3S)-derivs., composed of the regions between the P3 and P2' sites, showed enough inhibitory activity toward HIV-1 PR to become prototypes for further structural modification. Systematic replacement at the sites from P3 to P2' revealed that some bicyclic heteroarylcarbonyl derivs. possessed strong potency and good enzyme selectivity.

IT **139694-65-8P 141171-80-4P 141171-82-6P**
141269-68-3P 144779-91-9P 144780-27-8P
144780-28-9P 144780-29-0P 144780-31-4P
144780-33-6P 144780-35-8P 144780-36-9P
144780-37-0P 144780-40-5P 144780-41-6P

144830-02-4P 144830-03-5P 160778-10-9P
160778-11-0P 160778-12-1P 160778-13-2P
160866-63-7P 160866-64-8P 160866-65-9P
160866-66-0P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(structure-activity relationships of HIV-1 protease inhibitors contg. aminohydroxyphenylbutanoic acid)

L37 ANSWER 10 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:691727 CAPLUS
DOCUMENT NUMBER: 121:291727
TITLE: Structure-activity relationships of HIV protease inhibitors containing hydroxymethylcarbonyl isostere as a transition state mimic
AUTHOR(S): Mimoto, Tsutomu; Imai, Junya; Kisanuki, Sumitsugu; Hattori, Naoko; Takahashi, Osamu; Enomoto, Hiroshi; Akaji, Kenichi; Kiso, Yoshiaki
CORPORATE SOURCE: Dep. Med. Chem., Kyoto Pharmaceutical Univ., Kyoto, 607, Japan
SOURCE: Pept. 1992, Proc. Eur. Pept. Symp., 22nd (1993), Meeting Date 1992, 631-2. Editor(s): Schneider, Conrad H.; Eberle, Alex N. ESCOM: Leiden, Neth. CODEN: 60LUAN
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review with 5 refs. The lead optimization of the tripeptide compds. KNI 102, KNI 272, and KNI 227 is discussed. The optimized KNI compds. exhibit potent HIV-1 protease inhibitory activities and excellent selectivities against other aspartic proteases.
IT **139694-65-8**, KNI 102
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(structure-activity relationships of HIV-1 protease inhibitors contg. hydroxymethylcarbonyl isostere as a transition state mimic)

L37 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:631331 CAPLUS
DOCUMENT NUMBER: 121:231331
TITLE: Synthesis of hybrid type of anti-HIV drugs
AUTHOR(S): Uchiyama, Taketo; Asagarasu, Akira; Maruyama, Yasufumi; Achiwa, Kazuo
CORPORATE SOURCE: Sch. Pharm. Sci., Univ. Shizuoka, Shizuoka, 422, Japan
SOURCE: Pept. Chem. (1993), 31st, 89-92
CODEN: PECHDP; ISSN: 0388-3698
DOCUMENT TYPE: Journal
LANGUAGE: English
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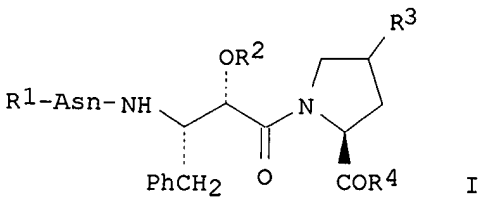

I

AB A report from a symposium on the syntheses and anti-HIV activity of peptide derivs. I [R1 = PhCH2O2C, PhOCH2CO, 3-O2NC6H4OCH2CO, MeO2CCO-Pro-D-Phe, MeO2CCO-Pro-Phe, 3-(MeO2CCO-Pro-D-Phe-NH)C6H4OCH2CO; R2

= H, COCO-Pro-D-Phe-OCH2Ph, MeO2CCO-Pro-D-Phe; R3 = H, OH, MeO2CCO-Pro-D-Phe; R4 = CMe3, CMe2CH2NHCO2CMe3, CMe2CH2NH2.HCl] having binding blockers which can bind to gp120 linked to an HIV protease inhibitor.

IT **139694-65-8P 153290-12-1P 158221-95-5P 158221-96-6P 158221-97-7P 158221-98-8P 158221-99-9P 158222-03-8P 158341-22-1P 158341-23-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and anti-HIV activity of)

L37 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:502890 CAPLUS
DOCUMENT NUMBER: 121:102890
TITLE: Solution structure of HIV-1 protease-allophenylnorstatine derivative inhibitor complex obtained from molecular dynamics simulation
AUTHOR(S): Kato, Ryohei; Takahashi, Osamu; Kiso, Yoshiaki; Moriguchi, Ikuo; Hirono, Shuichi
CORPORATE SOURCE: Sch. Pharm. Sci., Kitasato Univ., Tokyo, 108, Japan
SOURCE: Chem. Pharm. Bull. (1994), 42(1), 176-8
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Structures of 2 enzyme-inhibitor complexes of human immunodeficiency virus-1 protease with allophenylnorstatine derivs. were obtained from mol. dynamics simulation in aqs. soln. The stronger inhibitor gave considerably smaller fluctuation at P3 site, which formed H bonding with the enzyme flap region.

IT **139694-65-8D**, KNI 102, complexes with HIV-1 protease
RL: PRP (Properties)
(structure of, mol. dynamics simulation of)

L37 ANSWER 13 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:499067 CAPLUS
DOCUMENT NUMBER: 121:99067
TITLE: Structure-activity relationships of tripeptide HIV protease inhibitors containing the hydroxymethylcarbonyl isostere
AUTHOR(S): Enomoto, Hiroshi; Mimoto, Tsutomu; Kisanuki, Sumitsugu; Kimura, Tooru; Hattori, Naoko; Kageyama, Seiji; Mitsuya, Hiroaki; Akaji, Kenichi; Kiso, Yoshiaki
CORPORATE SOURCE: Dep. Med. Chem., Kyoto Pharm. Univ., Kyoto, 607, Japan
SOURCE: Pept. Chem. (1993), 31st, 181-4
CODEN: PECHDP; ISSN: 0388-3698
DOCUMENT TYPE: Journal
LANGUAGE: English
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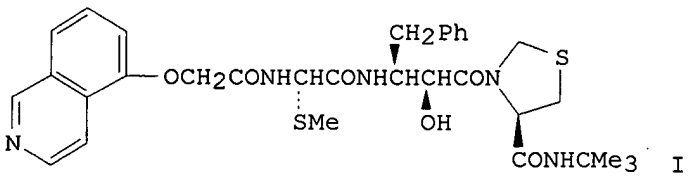

I

AB The inhibitors which had substitution of amino acid at P2 and/or P1 position of KNI-272 (I) with more lipophilic or hydrophilic residues were examd. in an enzyme inhibitory assay and antiviral assay. All the compds. inhibited HIV protease as strongly as I, but there was a difference in

antiviral activities of those compds. Low antiviral activities were shown by more hydrophilic compds. than I, while more lipophilic ones showed potent activities comparable to I.

IT **138258-64-7**, KNI 93 **139694-65-8**, KNI 102
RL: BIOL (Biological study)
(HIV-1 protease inhibitor, structure in relation to)

L37 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:23086 CAPLUS
DOCUMENT NUMBER: 120:23086
TITLE: Structure-activity relationships of HIV protease inhibitors containing allophenylnorstatin as a transition-state mimic
AUTHOR(S): Kisanuki, Sumitsugu; Mimoto, Tsutomu; Imai, Junya; Enomoto, Hiroshi; Hattori, Naoko; Takahashi, Osamu; Katoh, Ryohei; Tanaka, Shigeki; Sakikawa, Hiroshi; et al.
CORPORATE SOURCE: Dep. Med. Chem., Kyoto Pharm. Univ., Kyoto, 607, Japan
SOURCE: Pept. Chem. 1992, Proc. Jpn. Symp., 2nd (1993), Meeting Date 1992, 439-41. Editor(s): Yanaihara, Noboru. ESCOM: Leiden, Neth.
CODEN: 59NTAC
DOCUMENT TYPE: Conference
LANGUAGE: English

AB Replacement of subsites in KNI-102 (Z-Asn-Apns-Pro-NHBu-tert) (Apns = allophenylnorstatin) was carried out to det. the structural requirement of good activity at each subsite.

IT **139694-65-8**, KNI 102
RL: BIOL (Biological study)
(subsites replacement of, in study of structure-activity relationships of HIV protease inhibitors)

L37 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1993:462471 CAPLUS
DOCUMENT NUMBER: 119:62471
TITLE: In vitro anti-human immunodeficiency virus (HIV) activities of transition state mimetic HIV protease inhibitors containing allophenylnorstatine
AUTHOR(S): Kageyama, Seiji; Mimoto, Tsutomu; Murakawa, Yohko; Nomizu, Motoyoshi; Ford, Harry, Jr.; Shirasaka, Takuma; Gulnik, Sergei; Erickson, John; Takada, Kanji; et al.
CORPORATE SOURCE: Med. Branch, Natl. Cancer Inst., Bethesda, MD, 20892, USA
SOURCE: Antimicrob. Agents Chemother. (1993), 37(4), 810-17
CODEN: AMACCQ; ISSN: 0066-4804
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Transition state mimetic tripeptide human immunodeficiency virus (HIV) protease inhibitors contg. allophenylnorstatine [(2S,3S)-3-amino-2-hydroxy-4-phenylbutyric acid] were tested for activity against HIV in vitro. Two compds., KNI-227 and KNI-272, which were highly potent against HIV protease with little inhibition of other aspartic proteases, showed the most potent activity against the infectivity and cytopathic effect of a wide spectrum of HIV strains. As tested in target CD4+ ATH8 cells, the 50% inhibitory concns. of KNI-227 against HIV type 1 LAI (HIV-1LAI), HIV-1RF, HIV-1MN, and HIV-2ROD were 0.1, 0.02, 0.03, and 0.1 .mu.M, resp., while those of KNI-272 were 0.1, 0.02, 0.04, and 0.1 .mu.M, resp. Both agents completely blocked the replication of 3'-azido-2',3'-dideoxythymidine-sensitive and -insensitive clin. HIV-1 isolates at 0.08 .mu.M as tested in target phytohemagglutinin-activated peripheral blood mononuclear cells. The ratios of 50% cytotoxic concns. to 50% inhibitory concns. for KNI-227 and KNI-272 were .apprx.2,500 and >4,000, resp., as assessed in peripheral blood mononuclear cells. Both compds. blocked the

posttranslational cleavage of the p55 precursor protein to generate the mature p24 Gag protein in stably HIV-1-infected cells. The n-octanol-water partition coeffs. of KNI-227 and KNI-272 were high, with log P0/w values of 3.79 and 3.56, resp. Degrdn. of KNI-227 and KNI-272 in the presence of pepsin (1 mg/mL, pH 2.2) at 37.degree. for 24 h was negligible. Current data warrant further careful investigations toward possible clin. application of these two novel compds.

IT **139694-65-8**, KNI 102 **141171-77-9**, KNI 144
141171-80-4, KNI 153 **143909-16-4**, KNI 091
RL: BIOL (Biological study)
(human immunodeficiency virus inhibition by, in human cells, as protease inhibitor)

L37 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1993:204690 CAPLUS
DOCUMENT NUMBER: 118:204690
TITLE: Kynostatin (KNI)-227 and -272, highly potent anti-HIV agents: conformationally constrained tripeptide inhibitors of HIV protease containing allophenylnorstatine
AUTHOR(S): Mimoto, Tsutomu; Imai, Junya; Kisanuki, Sumitsugu; Enomoto, Hiroshi; Hattori, Naoko; Akaji, Kenichi; Kiso, Yoshiaki
CORPORATE SOURCE: Dep. Med. Chem., Kyoto Pharm. Univ., Kyoto, 607, Japan
SOURCE: Chem. Pharm. Bull. (1992), 40(8), 2251-3
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Selective and potent HIV protease inhibitors contg. allophenylnorstatine [Apns; (2S,3S)-3-amino-2-hydroxy-4-phenylbutyric acid] as a transition-state mimic were designed and synthesized. Among them, conformationally constrained tripeptide derivs., kynostatin (KNI)-227 and -272 exhibited highly potent antiviral activities against a wide spectrum of HIV isolates. Ready availability due to the simple synthetic procedure and the excellent antiviral properties indicate that KNI-227 and KNI-272 are promising candidates as selective anti-AIDS drugs.

IT **139694-65-8 141171-77-9**, KNI 144 **141171-80-4**
143934-32-1 143934-35-4 143934-36-5
143934-41-2 143934-43-4 147384-71-2
RL: BIOL (Biological study)
(HIV protease inhibiting activity of, structure in relation to)

L37 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1992:408449 CAPLUS
DOCUMENT NUMBER: 117:8449
TITLE: Design and synthesis of HIV protease inhibitors containing a hydroxymethylcarbonyl isostere as a transition-state mimic
AUTHOR(S): Mimoto, Tsutomu; Imai, Junya; Kisanuki, Sumitsugu; Tanaka, Shigeki; Hattori, Naoko; Takahashi, Osamu; Katoh, Ryohei; Yumisaki, Takuya; Sakikawa, Hiroshi; et al.
CORPORATE SOURCE: Dep. Med. Chem., Kyoto Pharm. Univ., Kyoto, 607, Japan
SOURCE: Pept. Chem. (1992), Volume Date 1991, 29th, 395-400
CODEN: PECHDP; ISSN: 0388-3698
DOCUMENT TYPE: Journal
LANGUAGE: English
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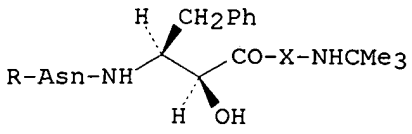

I

AB A report from a symposium on the prepn. and anti-HIV activity of allophenylnorstatine-proline tripeptide inhibitors, e.g. I (R = PhCO2O2C, X = Pro; R = 2-C10H7OCH2CO, X = L-5,5-dimethylthiazolidine-4-carboxylic acid).

IT **139694-65-8P**, KNI 102
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and HIV-1 protease inhibitory activity of)

L37 ANSWER 18 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1992:143332 CAPLUS
DOCUMENT NUMBER: 116:143332
TITLE: KNI-102, a novel tripeptide HIV protease inhibitor containing allophenylnorstatine as a transition-state mimic
AUTHOR(S): Mimoto, Tsutomu; Imai, Junya; Tanaka, Shigeki; Hattori, Naoko; Kisanuki, Sumitsugu; Akaji, Kenichi; Kiso, Yoshiaki
CORPORATE SOURCE: Dep. Med. Chem., Kyoto Pharm. Univ., Kyoto, 607, Japan
SOURCE: Chem. Pharm. Bull. (1991), 39(11), 3088-90
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English

AB HIV-1 protease inhibitors contg. allophenylnorstatine[Apns; (2S,3S)-3-amino-2-hydroxy-4-phenylbutyric acid]-Pro (syn diastereomer) as a transition-state mimic were established to be potent and highly selective. Z-Asn-Apns-Pro-NHBut (KNI-102) is the only tripeptide exhibiting substantial anti-HIV activity and may be of min. size for potent, selective inhibition of HIV protease. Ready availability due to its simple chem. structure and stability should make it valuable for studies of the development of metabolically stable anti-AIDS drugs.

IT **138228-18-9**, KNI 122 **138228-19-0 138228-20-3**
138258-64-7, KNI 93 **139694-65-8**, KNI 102
139694-67-0 139757-45-2 139758-09-1, KNI 81
139758-10-4 139758-12-6
RL: BIOL (Biological study)
(as HIV protease inhibitor, structure in, antiviral activity in relation to)

L37 ANSWER 19 OF 19 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1992:42041 CAPLUS
DOCUMENT NUMBER: 116:42041
TITLE: Rational design and synthesis of a novel class of active site-targeted HIV protease inhibitors containing a hydroxymethylcarbonyl isostere. Use of phenylnorstatine or allophenylnorstatine as a transition-state mimic
AUTHOR(S): Mimoto, Tsutomu; Imai, Junya; Tanaka, Shigeki; Hattori, Naoko; Takahashi, Osamu; Kisanuki, Sumitsugu; Nagano, Yuichi; Shintani, Makoto; Hayashi, Hideya; et al.
CORPORATE SOURCE: Dep. Med. Chem., Kyoto Pharm. Univ., Kyoto, 607, Japan
SOURCE: Chem. Pharm. Bull. (1991), 39(9), 2465-7
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English

Searched by Edward Hart 305-9203

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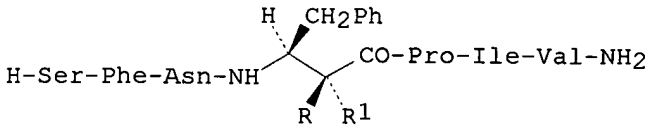

I

AB A novel class of HIV-1 protease inhibitors contg. a hydroxymethylcarbonyl isostere were designed from the substrate transition state and synthesized. Phenylnorstatine [(2R,3S)-3-amino-2-hydroxy-4-phenylbutyric acid] and the 2S diastereomer were effective transition-state mimics, and incorporation at the P1-P1' site gave potent and specific HIV-1 protease inhibitors I [R = H, R1 = OH (KNI-122); R = OH, R1 = H (KNI-93)]. In the inhibitory assays, the chem. synthesized [Ala67,95]HIV-1 protease was used.

IT **138228-18-9P 138228-19-0P 138228-20-3P**
138258-64-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and HIV-1 protease and porcine pepsin inhibitory activity of)

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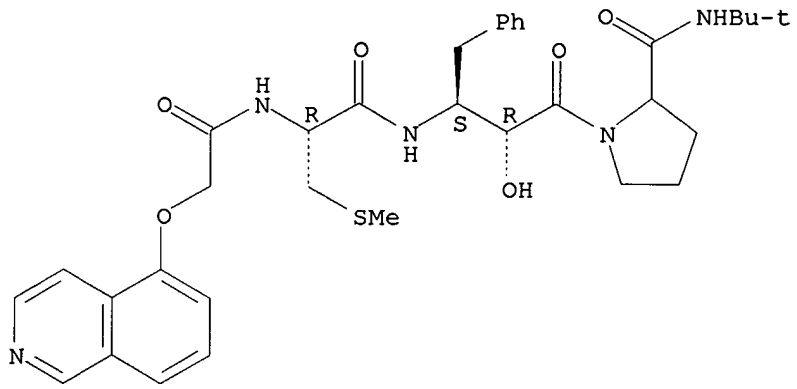
86 RN **143909-16-4** REGISTRY
87 RN **141269-68-3** REGISTRY
88 RN **141171-82-6** REGISTRY
89 RN **141171-80-4** REGISTRY
90 RN **141171-77-9** REGISTRY
91 RN **139758-12-6** REGISTRY
92 RN **139758-10-4** REGISTRY
93 RN **139758-09-1** REGISTRY
94 RN **139757-45-2** REGISTRY
95 RN **139694-67-0** REGISTRY
96 RN **139694-65-8** REGISTRY
97 RN **138258-64-7** REGISTRY
98 RN **138228-20-3** REGISTRY
99 RN **138228-19-0** REGISTRY
DR 139694-66-9
100 RN **138228-18-9** REGISTRY

=> d ide can 1 10 20 30 40 50 60 70 80 90 100

L38 ANSWER 1 OF 100 REGISTRY COPYRIGHT 2000 ACS
RN **194412-28-7** REGISTRY
CN Prolinamide, N-[(5-isoquinolinyloxy)acetyl]-S-methyl-L-cysteinyl-(2R,3S)-2-hydroxy-4-phenyl-3-aminobutanoyl-N-(1,1-dimethylethyl)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C34 H43 N5 O6 S
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.

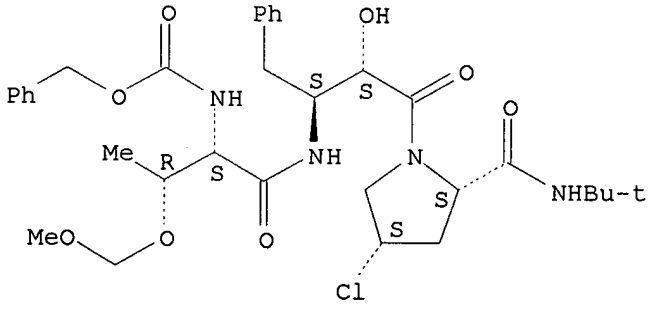


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:195514

L38 ANSWER 10 OF 100 REGISTRY COPYRIGHT 2000 ACS
RN **180266-20-0** REGISTRY
CN L-Prolinamide, O-(methoxymethyl)-N-[(phenylmethoxy)carbonyl]-L-threonyl-(.alpha.S,.beta.S)-.beta.-amino-.alpha.-hydroxybenzenebutanoyl-4-chloro-N-(1,1-dimethylethyl)-, (4S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Prolinamide, O-(methoxymethyl)-N-[(phenylmethoxy)carbonyl]-L-threonyl-(2S,3S)-2-hydroxy-4-phenyl-3-aminobutanoyl-4-chloro-N-(1,1-dimethylethyl)-, cis-
FS STEREOSEARCH
MF C33 H45 Cl N4 O8
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

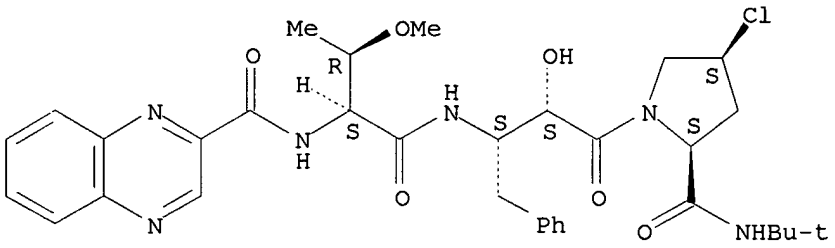
REFERENCE 1: 128:149570

REFERENCE 2: 125:168657

L38 ANSWER 20 OF 100 REGISTRY COPYRIGHT 2000 ACS
RN **180266-06-2** REGISTRY
CN L-Prolinamide, O-methyl-N-(2-quinoxalinylcarbonyl)-L-threonyl-(.alpha.S,.beta.S)-.beta.-amino-.alpha.-hydroxybenzenebutanoyl-4-chloro-N-(1,1-dimethylethyl)-, (4S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:

CN L-Prolinamide, O-methyl-N-(2-quinoxalinylcarbonyl)-L-threonyl-(2S,3S)-2-hydroxy-4-phenyl-3-aminobutanoyl-4-chloro-N-(1,1-dimethylethyl)-, cis-
FS STEREOSEARCH
MF C33 H41 Cl N6 O6
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



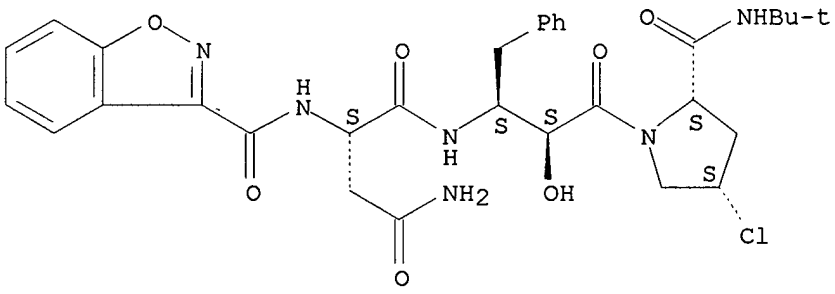
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 128:149570

REFERENCE 2: 125:168657

L38 ANSWER 30 OF 100 REGISTRY COPYRIGHT 2000 ACS
RN **166383-45-5** REGISTRY
CN L-Prolinamide, N2-(1,2-benzisoxazol-3-ylcarbonyl)-L-asparaginyl-(2S,3S)-2-hydroxy-4-phenyl-3-aminobutanoyl-4-chloro-N-(1,1-dimethylethyl)-, cis- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C31 H37 Cl N6 O7
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL

Absolute stereochemistry.



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

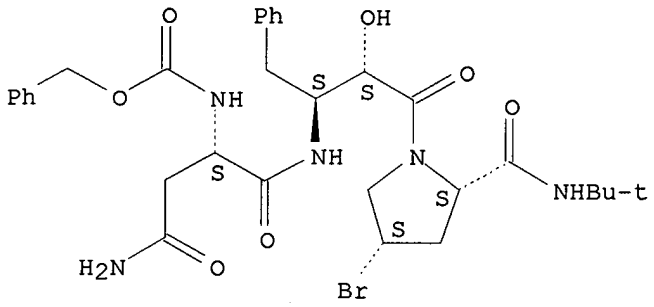
REFERENCE 1: 125:292240

REFERENCE 2: 123:144637

L38 ANSWER 40 OF 100 REGISTRY COPYRIGHT 2000 ACS
RN **166382-69-0** REGISTRY
CN L-Prolinamide, N2-[(phenylmethoxy)carbonyl]-L-asparaginyl-(2S,3S)-2-hydroxy-4-phenyl-3-aminobutanoyl-4-bromo-N-(1,1-dimethylethyl)-, cis- (9CI) (CA INDEX NAME)
FS STEREOSEARCH

MF C31 H40 Br N5 O7
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL

Absolute stereochemistry.



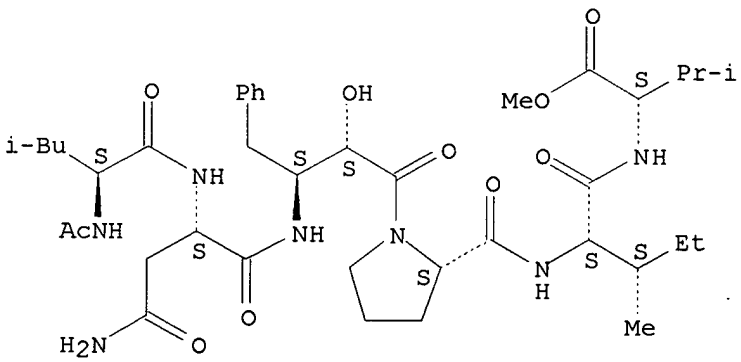
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 125:292240

REFERENCE 2: 123:144637

L38 ANSWER 50 OF 100 REGISTRY COPYRIGHT 2000 ACS
RN **160778-11-0** REGISTRY
CN L-Valine, N-acetyl-L-leucyl-L-asparaginyl-(2S,3S)-2-hydroxy-4-phenyl-3-aminobutanoyl-L-prolyl-L-isoleucyl-, methyl ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C39 H61 N7 O10
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



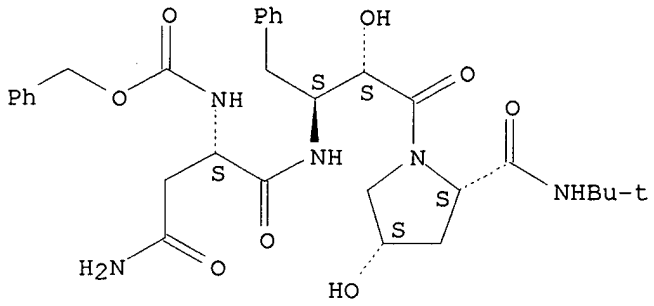
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 122:122508

L38 ANSWER 60 OF 100 REGISTRY COPYRIGHT 2000 ACS
RN **153380-13-3** REGISTRY
CN Carbamic acid, [3-amino-1-[[[3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-hydroxy-1-pyrrolidinyl]-2-hydroxy-3-oxo-1-(phenylmethyl)propyl]amino]carbonyl]-3-oxopropyl]-, phenylmethyl ester, [2S-[1[1R*(R*),2R*],2.alpha.,4.alpha.]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH

MF C31 H41 N5 O8
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL

Absolute stereochemistry.



3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

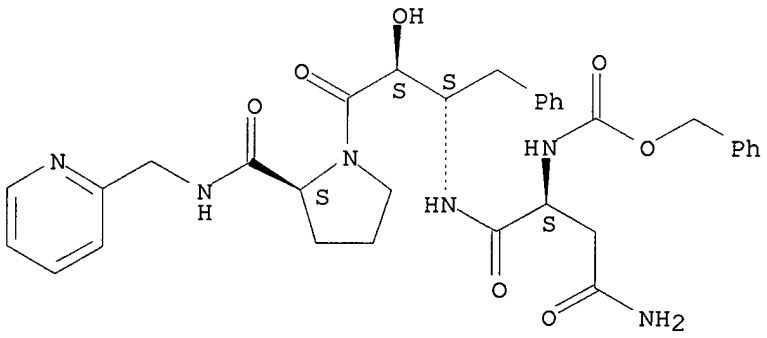
REFERENCE 1: 125:292240

REFERENCE 2: 123:144637

REFERENCE 3: 120:245776

L38 ANSWER 70 OF 100 REGISTRY COPYRIGHT 2000 ACS
RN **144780-35-8** REGISTRY
CN L-Prolinamide, N2-[(phenylmethoxy)carbonyl]-L-asparaginyl-(2S,3S)-2-hydroxy-4-phenyl-3-aminobutanoyl-N-(2-pyridinylmethyl)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C33 H38 N6 O7
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 122:122508

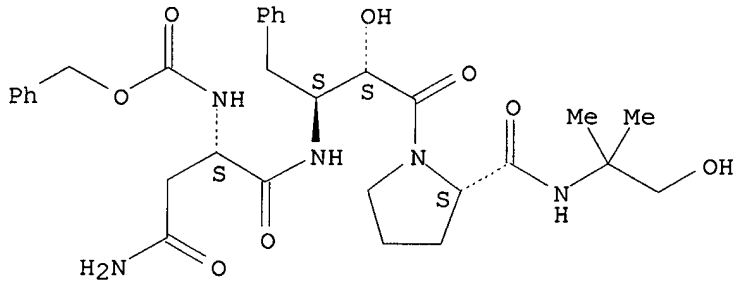
REFERENCE 2: 120:245776

REFERENCE 3: 118:22632

L38 ANSWER 80 OF 100 REGISTRY COPYRIGHT 2000 ACS

RN **143934-48-9** REGISTRY
CN L-Prolinamide, N2-[(phenylmethoxy)carbonyl]-L-asparaginyl-(2S,3S)-2-hydroxy-4-phenyl-3-aminobutanoyl-N-(2-hydroxy-1,1-dimethylethyl)- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C31 H41 N5 O8
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



4 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 125:11470

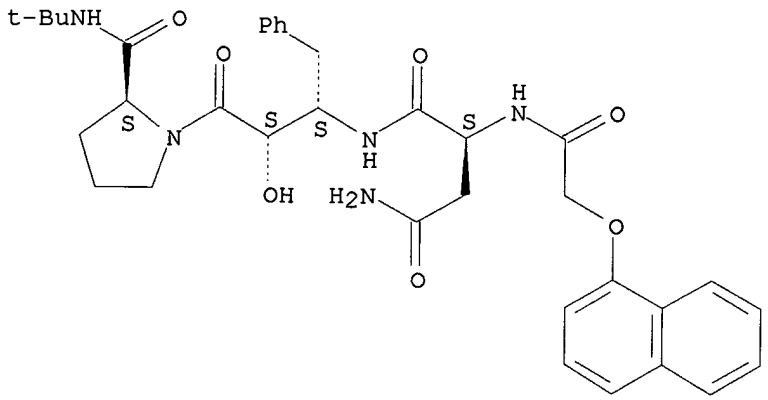
REFERENCE 2: 120:245776

REFERENCE 3: 119:9161

REFERENCE 4: 118:22632

L38 ANSWER 90 OF 100 REGISTRY COPYRIGHT 2000 ACS
RN **141171-77-9** REGISTRY
CN Butanediamide, N1-[3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2-hydroxy-3-oxo-1-(phenylmethyl)propyl]-2-[[(1-naphthalenyloxy)acetyl]amino]-, [2S-[1[1R*(R*),2R*],2R*]]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN KNI 144
FS STEREOSEARCH
MF C35 H43 N5 O7
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, TOXLIT
(*File contains numerically searchable property data)

Absolute stereochemistry.



6 REFERENCES IN FILE CA (1967 TO DATE)
6 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 120:289408

REFERENCE 2: 120:245776

REFERENCE 3: 119:62471

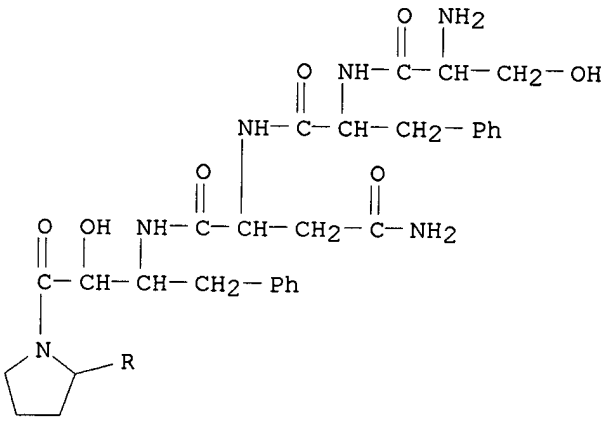
REFERENCE 4: 119:9161

REFERENCE 5: 118:204690

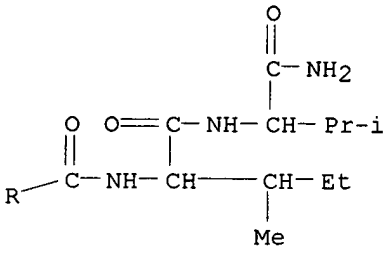
REFERENCE 6: 116:227702

L38 ANSWER 100 OF 100 REGISTRY COPYRIGHT 2000 ACS
RN **138228-18-9** REGISTRY
CN L-Valinamide, L-seryl-L-phenylalanyl-L-asparaginyl-(2R,3S)-2-hydroxy-4-phenyl-3-aminobutanoyl-L-prolyl-L-isoleucyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN KNI 122
FS PROTEIN SEQUENCE
MF C42 H61 N9 O10
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, TOXLIT
(*File contains numerically searchable property data)

PAGE 1-A



PAGE 2-A



3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 119:9161

REFERENCE 2: 116:143332

REFERENCE 3: 116:42041

=> file caplus

FILE 'CAPLUS' ENTERED AT 12:18:13 ON 06 NOV 2000
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1967 - 6 Nov 2000 VOL 133 ISS 20
FILE LAST UPDATED: 5 Nov 2000 (20001105/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

Now you can extend your author, patent assignee, patent information, and title searches back to 1907. The records from 1907-1966 now have this searchable data in CAOLD. You now have electronic access to all of CA: 1907 to 1966 in CAOLD and 1967 to the present in CAPLUS on STN.

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L5		STR
L7		STR
L11		STR
L15		STR
L17		STR
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L22	370	SEA FILE=REGISTRY SUB=L20 SSS FUL L5
L23	390	SEA FILE=REGISTRY SUB=L20 SSS FUL L7

Searched by Edward Hart 305-9203

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L25         168 SEA FILE=REGISTRY SUB=L20 SSS FUL L15
L26          93 SEA FILE=REGISTRY SUB=L20 SSS FUL L17
L27          12 SEA FILE=CAPLUS ABB=ON  PLU=ON  L21
L28          34 SEA FILE=CAPLUS ABB=ON  PLU=ON  L22
L29         100 SEA FILE=CAPLUS ABB=ON  PLU=ON  L23
L30          11 SEA FILE=CAPLUS ABB=ON  PLU=ON  L24
L31         527 SEA FILE=CAPLUS ABB=ON  PLU=ON  L25
L32         439 SEA FILE=CAPLUS ABB=ON  PLU=ON  L26
L33           2 SEA FILE=CAPLUS ABB=ON  PLU=ON  L27 AND L28 AND L29 AND L30
                AND L31 AND L32
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L37          19 SEA FILE=CAPLUS ABB=ON  PLU=ON  L36 NOT (2000 OR 1999 OR
                1998)/PY
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                OR 1999 OR 1998)/PY)
L40          10 SEA FILE=CAPLUS ABB=ON  PLU=ON  L39 AND PATENT/DT


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L40  ANSWER 1 OF 10  CAPLUS  COPYRIGHT 2000 ACS
ACCESSION NUMBER:         1996:228484  CAPLUS
DOCUMENT NUMBER:          124:290277
TITLE:                    HIV protease inhibitor combinations.
INVENTOR(S):              Barrish, Joel C.; Colonno, Richard J.; Lin, Pin-Fang
                          M.
PATENT ASSIGNEE(S):       Bristol-Myers Squibb Co., USA
SOURCE:                   Eur. Pat. Appl., 29 pp.
                          CODEN: EPXXDW
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   3
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
     EP 691345          A2   19960110       EP 1995-304718   19950705
     EP 691345          A3   19960228
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
     US 1649            H1   19970506       US 1995-436868   19950517
     AU 9524800         A1   19960118       AU 1995-24800    19950704
PRIORITY APPLN. INFO.:                      US 1994-270614   19940705
                                            US 1995-436868   19950517
                                            US 1987-79978    19870731

GI
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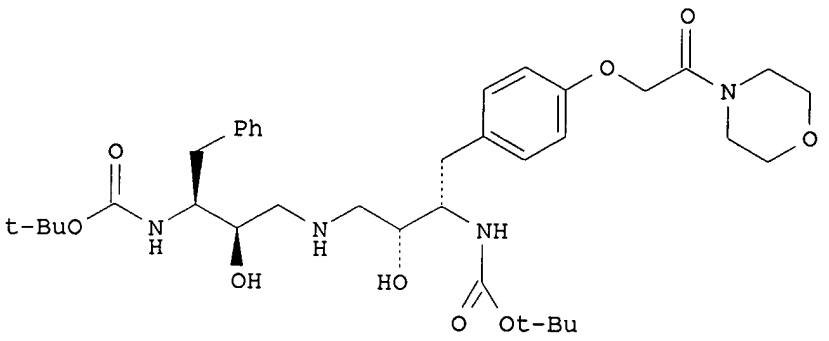

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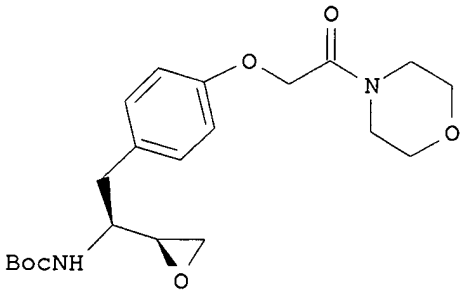

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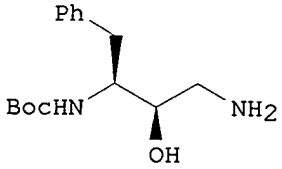


III

AB A product comprising HIV-1 protease inhibitor (I) (BMS-186318) and .gtoreq.1 of RO 31-8959, SC-52151, A-77003, A-80987, ABT-538, L-735,524, and AG-1343 is claimed. The combinations may eliminate or substantially reduce viral cross-resistance seen with use of individual HIV-1 protease inhibitors. A synthesis of I via coupling of epoxide (II) with aminoalc. (III) is given.

IT **134878-17-4**, A-77003
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HIV protease inhibitor combinations)

L40 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:810448 CAPLUS
DOCUMENT NUMBER: 123:218429
TITLE: Aspartyl proteinase inhibitor preparation, assay, and use for treatment of Alzheimer's Disease
INVENTOR(S): Dovey, Harry F.; John, Varghese; Laguzza, Bennett C.; Lieberberg, Ivan M.; Little, Sheila P.; Sinha, Sukanto
PATENT ASSIGNEE(S): Lilly, Eli, and Co., USA; Athena, Eli, and Co.
SOURCE: Can. Pat. Appl., 175 pp.
CODEN: CPXXEB
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2129689	AA	19950210	CA 1994-2129689	19940808
ZA 9405719	A	19960201	ZA 1994-5719	19940801
EP 652009	A1	19950510	EP 1994-305833	19940805
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
AU 9468970	A1	19950216	AU 1994-68970	19940808
HU 71515	A2	19951228	HU 1994-2312	19940808
CN 1120040	A	19960410	CN 1994-109527	19940808
PRIORITY APPLN. INFO.:			US 1993-104293	19930809

OTHER SOURCE(S): MARPAT 123:218429
AB .beta.-Amyloid peptide (.beta.AP) prodn. in cell culture and in vivo is inhibited by administering aspartyl protease inhibitors, particularly inhibitors of proteases of cathepsin D. Useful aspartyl protease inhibitors can be selected in a two-step assay, where test compds. are first screened for aspartyl protease inhibition activity in vitro in noncellular assays. Those test compds. which are found to display protease inhibition activity are then tested in cellular assay for .beta.AP prodn. inhibition. Those test compds. which are capable of inhibiting intracellular B-amyloid prodn. may be incorporated in pharmaceutical compns.
IT **134805-67-7P 140385-91-7P 144239-46-3P 168172-24-5P 168172-56-3P 168172-57-4P 168172-58-5P**
RL: ANT (Analyte); BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(aspartyl proteinase inhibitor prepn., assay, and use for treatment of Alzheimer's Disease)

L40 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:580830 CAPLUS
DOCUMENT NUMBER: 122:322518
TITLE: Pharmaceutical composition for parenteral, enteral and dermal administration of essentially insoluble drugs
INVENTOR(S): Reul, Bernhard; Petri, Walter; Winkler, Irvin
PATENT ASSIGNEE(S): Hoechst A.-G., Germany
SOURCE: Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
DOCUMENT TYPE: **Patent**
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 649660	A2	19950426	EP 1994-116552	19941020
EP 649660	A3	19960731		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
DE 4336434	A1	19950427	DE 1993-4336434	19931026
CA 2134293	AA	19950427	CA 1994-2134293	19941025
JP 07187995	A2	19950725	JP 1994-259928	19941025
PRIORITY APPLN. INFO.:			DE 1993-4336434	19931026

AB The title compn. contains a drug which is essentially insol. in water and lipophilic media and .gtoreq.1 physiol. acceptable amphosurfactant which is sol. or forms micellar-colloidal solns. in water, dissolved in an anhyd. water-miscible solvent. This soln. is mixed with water to form a metastable micellar-colloidal dispersion suitable for enteral or parenteral administration. Thus, a dispersion conc. contg. 95.7% HBY 793 5.73, epicholine 75 69.50, and glycofurol 75 480.77 was mixed with water 5000.00 mg to form a soln.
IT **137755-25-0**, HBY 793
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compn. for parenteral, enteral and dermal administration of essentially insol. drugs)

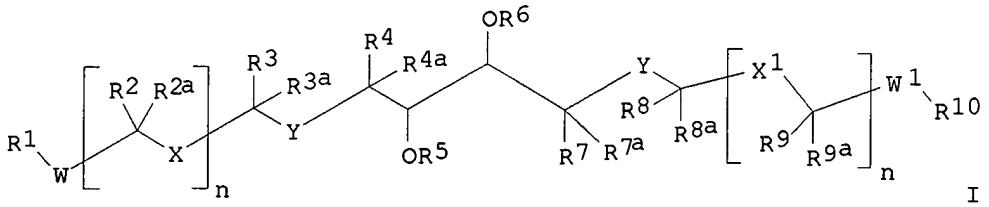
L40 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:701325 CAPLUS
DOCUMENT NUMBER: 121:301325
TITLE: 1,4-Diamino-2,3-dihydroxybutanes useful as antiviral agents
INVENTOR(S): Jadhav, Prabhakar K.; McGee, Lawrence R.; Shenvi, Ashok; Hodge, Carl N.

PATENT ASSIGNEE(S): DuPont Merck Pharmaceutical Co., USA
SOURCE: U.S., 75 pp. Cont.-in-part of U.S. Ser. No. 531,971, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5294720	A	19940315	US 1991-714042	19910531
CA 2084087	AA	19911202	CA 1991-2084087	19910531
HU 64738	A2	19940228	HU 1992-3505	19910531
EP 665215	A1	19950802	EP 1995-101007	19910531
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
ZA 9104194	A	19930224	ZA 1991-4194	19910603
NO 9204615	A	19930129	NO 1992-4615	19921130
US 5430155	A	19950704	US 1993-167659	19931217
AU 9516339	A1	19950817	AU 1995-16339	19950410

PRIORITY APPLN. INFO.:
US 1990-531971 19900601
EP 1991-912877 19910531
US 1991-714042 19910531
WO 1991-US3852 19910531

OTHER SOURCE(S): MARPAT 121:301325
GI



I

AB Approx. 100 title compds. I [R1-R4, R7-R10 = H, (un)substituted alkyl, alkenyl, alkynyl, cycylalkyl, bicycloalkyl, aryl, carbocyclyl, heterocyclyl; R2a-R4a, R7a-R9a = H, alkyl or benzyl substituted by halo or alkoxy; R5, R6 = H, (un)substituted alkoxycarbonyl, alkylcarbonyl, PhCO, PhOCO, PhNHCO; W, W1, X, X1 = various bivalent linking groups; Y, Y1 = various N-contg. bivalent groups; n = 0, 1] were prepd. For example, amidation of Boc-Phe-OH (Boc = tert-butoxycarbonyl) with MeNHOMe.HCl using ClCO2Bu-iso/N-methylmorpholine/Et3N gave Boc-Phe-NMeOMe, which was reduced with LiAlH4 in Et2O to give the aldehyde (S)-PhCH2CH(NH-Boc)CHO. Coupling of this using Caulton's reagent in DMF gave the diol PhCH2CH(NH-Boc)CH(OH)CH(OH)CH(NH-Boc)CH2Ph (II) as a mixt. of its (S,S,S,S)-, (S,R,R,S)-, and (S,S,R,S)-isomers. In an assay for prevention of HIV-induced cell death, (S,S,S,S)- and (S,R,R,S)-I had relative IC90 values of 30 and 3.0. The latter isomer was also prepd. from D-mannitol by 2 methods using cuprate addn. and azide steps (caution - azides potentially explosive).

IT **134805-64-4P 134805-65-5P 140196-55-0P**
140196-60-7P 140196-62-9P 140196-64-1P
140196-65-2P 140196-66-3P 140196-67-4P
140196-68-5P 140196-69-6P 140196-70-9P
140196-71-0P 140196-72-1P 140196-73-2P
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140196-77-6P 140196-79-8P 140196-80-1P
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140196-93-6P 140196-94-7P 140196-95-8P
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140197-02-0P 140197-03-1P 140197-04-2P
140197-05-3P 140197-06-4P 140210-85-1P
140210-86-2P 140210-87-3P 140210-88-4P
140210-90-8P 140210-91-9P 140210-92-0P
140210-93-1P 140210-94-2P 140385-88-2P
140385-89-3P 140385-90-6P 140385-91-7P
140385-92-8P 140386-97-6P 140386-98-7P
140386-99-8P 140459-61-6P 140459-62-7P
158894-24-7P 158894-25-8P 158894-26-9P
158999-67-8P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as antiviral agent)

IT **140385-89-3**
RL: RCT (Reactant)
(reaction of, in prepn. of diaminodihydroxybutane derivs. as antiviral agents)

L40 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:191116 CAPLUS
DOCUMENT NUMBER: 120:191116
TITLE: Process for the preparation of a substituted diaminodiol
INVENTOR(S): Sowin, Thomas J.; Hannick, Steven M.; Doherty, Elizabeth M.; Sato, Takahiro; Suzuki, Takayuki
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9323361	A1	19931125	WO 1993-US4403	19930510

W: CA, JP
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRIORITY APPLN. INFO.: US 1992-885575 19920519
OTHER SOURCE(S): MARPAT 120:191116
AB Title compds. (I; PhCH2CH(R3NH)CH(OH)CH(OH)CH(R3NH)CH2Ph) (wherein R3 = H, N-protectant) useful as HIV protease inhibitor (no data), are prepd. L-Phenylalamine Me ester-HCl (prepn. given) in CHCl3 was cooled to 0.degree., Na2CO3 was added followed by ClCO2CH2Ph to give the benzoyloxycarbony deriv., which was treated with LiAlH4 to the alaninol, treated with (COCl)2 to give the alaninal and in turn reacted with VCl3(THF)3 and Zn dust to give a mixt. of diols which were treated with acetone and concd. H2SO4 to give (2S,3R,4R,5S)-I (R3 = PhCH2O2C).
IT **134878-17-4P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as HIV protease inhibitor)

L40 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:55011 CAPLUS
DOCUMENT NUMBER: 120:55011
TITLE: Process for the diastereoselective reductive pinacol coupling of homochiral alpha-aminoaldehydes
INVENTOR(S): Jacobi, Detlef; Jendralla, Heiner; Kammermeier,

	Bernhard
PATENT ASSIGNEE(S):	Hoechst A.-G., Germany
SOURCE:	Can. Pat. Appl., 46 pp.
	CODEN: CPXXEB
DOCUMENT TYPE:	**Patent**
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2079953	AA	19930408	CA 1992-2079953	19921006
EP 541946	A1	19930519	EP 1992-116761	19920930
EP 541946	B1	19960717		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, PT, SE				
AT 140449	E	19960815	AT 1992-116761	19920930
NO 9203879	A	19930413	NO 1992-3879	19921006
JP 05239000	A2	19930917	JP 1992-267159	19921006
HU 63607	A2	19930928	HU 1992-3163	19921006
US 5463124	A	19951031	US 1994-264842	19940622
PRIORITY APPLN. INFO.:			DE 1991-4133202	19911007
			US 1992-956238	19921005

OTHER SOURCE(S): CASREACT 120:55011; MARPAT 120:55011

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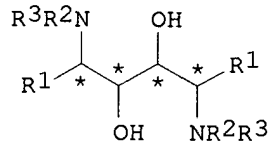

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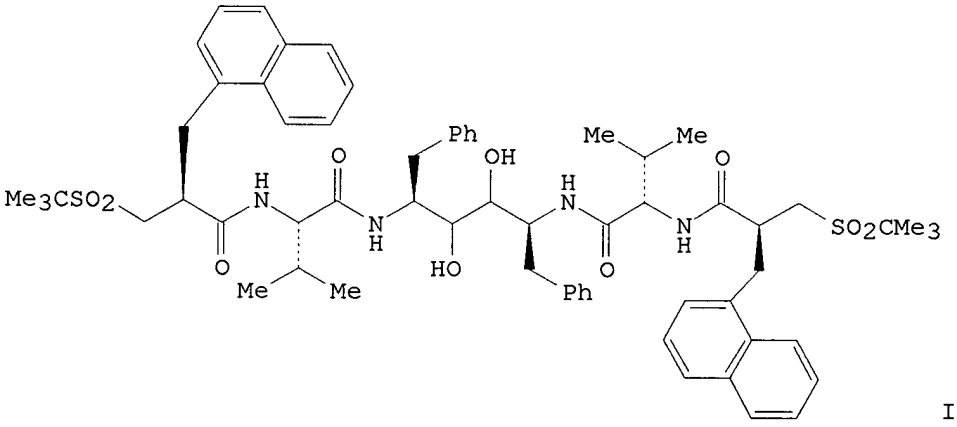

II

AB Sym. title compds. [I; R1 = .alpha.-amino acid side chain; R2, R3 = H, DEnFoGp; E, F, G = (un)natural amino acid residue, -azaamino acid residue, -imino acid residue; n, o, p = 0, 1; D = R4, R4R5NCR6R7CO, R5OCHR6CO, etc.; R4 = H, carboxyl, (substituted) alkyl; mono-, bi-, or tricyclic cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, aryloxyalkyl, arylcycloalkyl, heterocyclyl, etc.; R5, R7 = H, alkyl; R6 = R4, OH, alkanoyloxy, etc.], were prepd. with control over the chirality of the 4 chiral centers by treating homochiral R1(R3R2N)CHCHO with NbCl3.dimethoxyethane complex. Thus, title compd. II was prepd. by refluxing 1 equiv of the corresponding aldehyde with 1.4 equiv complex in THF.

IT **137755-25-0P 145631-95-4P**

RL: SPN (Synthetic preparation); PREP (Preparation)

(prepn. of, by niobium trichloride dimethoxyethane etherate-mediated

pinacol coupling)

L40 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1993:538493 CAPLUS
DOCUMENT NUMBER: 119:138493
TITLE: Process for diastereoselective reductive pinacol coupling of homochiral .alpha.-amino aldehydes
PATENT ASSIGNEE(S): Hoechst A.-G., Germany
SOURCE: Ger. Offen., 22 pp.
CODEN: GWXXBX
DOCUMENT TYPE: **Patent**
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4122885	A1	19930121	DE 1991-4122885	19910711

OTHER SOURCE(S): CASREACT 119:138493; MARPAT 119:138493
AB Optically pure sym. diamino diols [R3R2NCH(R1)CH(OH)]2 [R1 = sidechain of a natural or unnatural amino acid; R2, R3 = H, numerous extensively defined groups] are prepd. with simultaneous control of all 4 chiral centers by reductive pinacol coupling of homochiral .alpha.-amino aldehydes R3R2NCH(R1)CHO using either [V2Cl3(THF)6]2[Zn2Cl6] or a V complex prepd. in situ from VCl3, THF, and Zn dust. For example, VCl3(THF)3 in CH2Cl2 was treated with Zn dust, then with O:P(NMe2)3 [complex former], and finally with 5 g N-(tert-butoxycarbonyl)-(S)-phenylalaninal (prepn. given) to give N,N'-bis(tert-butoxycarbonyl)-2,5-diamino-1,6-diphenylhexane-3,4-diol (I). The product was sepd. to give 3.3 g pure (2S,3R,4R,5S)-I, and 0.8 g mixed (2S,3S,4S,5S)- and (2S,3R,4S,5S)-I. Six addnl. coupling examples are described.
IT **129467-48-7P 145631-95-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, by stereoselective reductive pinacol coupling)

L40 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1993:234482 CAPLUS
DOCUMENT NUMBER: 118:234482
TITLE: Preparation of diaminodihydroxyalkanes and amino acid and peptide derivatives thereof as retroviral protease inhibitors
INVENTOR(S): Dreyer, Geoffrey Bainbridge; Boehm, Jeffrey Charles
PATENT ASSIGNEE(S): SmithKline Beecham Corp., USA
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9200948	A1	19920123	WO 1991-US4756	19910703
W: AU, CA, JP, KR, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
AU 9183206	A1	19920204	AU 1991-83206	19910703
EP 538396	A1	19930428	EP 1991-914409	19910703
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 06501681	T2	19940224	JP 1991-513325	19910703
ZA 9105271	A	19920527	ZA 1991-5271	19910708
PRIORITY APPLN. INFO.:			US 1990-549456	19900706
			WO 1991-US4756	19910703

OTHER SOURCE(S): MARPAT 118:234482
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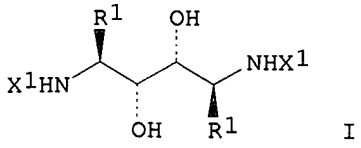

I

AB Title compds. [I; X1 = ABn; n = 0-2; B = Ala, Asn, Cys, Trp, Gly, Gln, Ile, Leu, Met, Phe, Pro, Ser, Thr, Tyr, Val, His, trifluoroalanyl; A = Ph3C, H, alkyl, CHO, (HO-, Cl-, or F-substituted) acyl, (substituted) benzoyl, naphthoyl, heterocyclylcarbonyl, phthaloyl, etc.; R1 = CH2R12, H, (HO-, Cl-, F-substituted) alkyl, cycloalkyl; R12 = NHA, R5(R6R7C)m, (substituted) (benz)imidazolyl, R8SOn, (R13O)P(O)(OR14), etc.; R5, R6, R7 = H, Cl, F, (substituted) alkyl, Ph, naphthyl, alkoxy, heterocyclyl; R5R6R7 = atoms to complete mono-, bi-, or tricycloalkyl; R8 = 5-7-membered heterocyclyl; R13, R14 = H, (cyclo)alkyl, R8, (substituted) amino, (benz)imidazolyl, alkenyl, alkynyl, etc.], were prepd. Thus, (2S,3R,4R,5S)-1,2:5,6-di-(N-carbobenzyloxyimino)-3,4-(O-isopropylidene)hexanediol (prepd. from D-mannitol) in THF was added to a -60.degree. mixt. of LiBr, CuBr, and Me2CHMgBr in THF; the mixt. was stirred 2 h at -50.degree. and at -25.degree. overnight to give 27% (1S,32R,3R,4S)-carbobenzyloxy-N-[1-(2-methyl)propyl-2,3-(O-isopropylidenediol)-4-carbobenzyloxyamino-6-methyl]heptylamide. The product was hydrogenolyzed over Pd/C in MeOH followed by coupling with carbobenzyloxyalanylalanine using DCC and hydroxybenzotriazole and deprotection with 70% HOAc at 50.degree. to give I (X1 = carbobenzyloxyalanylalanyl, R1 = Me2CHCH2) (II). II inhibited rHIV-1 protease with Ki = 0.58 .mu.M.

IT **129467-48-7P 142285-33-4P 142285-34-5P**
142285-35-6P 142285-36-7P 142285-39-0P
142285-40-3P 142285-41-4P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of, as retroviral protease inhibitor)

L40 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1992:490809 CAPLUS
DOCUMENT NUMBER: 117:90809
TITLE: Peptides containing substituted 1,4-diamines as transition-state inserts
INVENTOR(S): Thaisrivongs, Suvit
PATENT ASSIGNEE(S): Upjohn Co., USA
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9206996	A1	19920430	WO 1991-US7047	19911001
W: AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MC, MG, MN, MW, NO, PL, RO, SD, SU, US				
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
AU 9187594	A1	19920520	AU 1991-87594	19911001
EP 552247	A1	19930728	EP 1991-918640	19911001
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 06502403	T2	19940317	JP 1991-517923	19911001
PRIORITY APPLN. INFO.:			US 1990-595470	19901010

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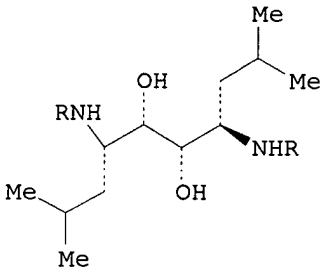
US 1990-595740 19901010
WO 1991-US7047 19911001

OTHER SOURCE(S): MARPAT 117:90809
GI



I

AB Title peptides, including I (R = Me3CO2C, Me3CO2C-Val, Noa-His; Noa = 1-naphthyloxacetyl) and their stereoisomers were prepd. as anti-HIV virucides. Thus, I (R = Me3CO2C-Val) was obtained in 7 steps from Me2CHCH2CH2COCl and inhibited HIV protease activity at 0.65 nM.

IT **143642-47-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and acylation of)

IT **142589-95-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and deblocking of)

IT **142589-96-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and detosylation of)

IT **142285-40-3P 142589-94-4P 142589-97-7P**
142695-65-6P 142695-67-8P 142695-68-9P
142695-69-0P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and virucidal activity of)

L40 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1992:194884 CAPLUS
DOCUMENT NUMBER: 116:194884
TITLE: 1,4-Diamino-2,3-dihydroxybutanes
INVENTOR(S): Jadhav, Prabhakar Kondaji; McGee, Lawrence Ray; Shenvi, Ashok; Hodge, Carl Nicholas
PATENT ASSIGNEE(S): Du Pont Merck Pharmaceutical Co., USA
SOURCE: PCT Int. Appl., 244 pp.
CODEN: PIXXD2
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9118866	A2	19911212	WO 1991-US3852	19910531
WO 9118866	A3	19920430		
W: AU, BB, BG, BR, CA, FI, HU, JP, KP, KR, LK, NO, PL, NO, PL, RO, SU				
RW: AT, BE, BF, BJ, CF, CG, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
CA 2084087	AA	19911202	CA 1991-2084087	19910531
EP 532693	A1	19930324	EP 1991-912877	19910531
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
BR 9106540	A	19930525	BR 1991-6540	19910531
HU 64738	A2	19940228	HU 1992-3505	19910531

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     JP 07502970        T2    19950330       JP 1991-512068    19910531
     EP 665215          A1    19950802       EP 1995-101007    19910531
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE
     ZA 9104194         A     19930224       ZA 1991-4194      19910603
     NO 9204615         A     19930129       NO 1992-4615      19921130
PRIORITY APPLN. INFO.:                       US 1990-531971    19900601
                                             EP 1991-912877    19910531
                                             US 1991-714042    19910531
                                             WO 1991-US3852    19910531
OTHER SOURCE(S):          CASREACT 116:194884; MARPAT 116:194884
AB   The title compds. were prepd. by 3 methods: (1) reductive coupling of
     aldehydes with Coulton's reagent, [V2Cl3(THF)6]2[Zn2Cl6]; (2) reductive
     coupling of aldehydes with a catalyst obtained from VCl3(THF)3 and Zn-Cu;
     (3) from D-mannitol via cuprate addn.  Thus, N-(tert-butoxycarbonyl)-L-
     phenylalanine reacted with N-methylmorpholine, iso-Bu chloroformate,
     MeNHOMe.cntdot.HCl, and Et3N in CHCl3, and the product was reduced with
     LiAlH4 in Et2O to give PhCH2CH(NHBoc)CHO (I, Boc = CO2CMe3).  Treatment of
     I with Caulton's reagent in CH2Cl2-DMF gave (all-S)-
     PhCH2CH(NHBoc)CH(OH)CH(OH)CH(NHBoc)CH2Ph (II), which was treated with 4N
     HCl in dioxane to remove the Boc groups.  II protected MT-2 cells against
     strains of HIV with an IC50 of 10 mg/mL.
IT   134805-64-4P 134805-65-5P 140196-62-9P
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     140385-90-6P 140385-91-7P 140385-92-8P
     140385-93-9P 140386-97-6P 140386-98-7P
     140386-99-8P 140459-61-6P 140459-62-7P
     RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic
     preparation); BIOL (Biological study); PREP (Preparation)
        (prepn. and antiviral activity of)
IT   140385-89-3P
     RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
        (prepn. and reaction of, with adamantyl ethylene oxide)
IT   140196-55-0P 140196-60-7P 140210-93-1P
     140210-94-2P 140385-88-2P
     RL: SPN (Synthetic preparation); PREP (Preparation)
        (prepn. of)


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E143 THROUGH E238 ASSIGNED

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DICTIONARY FILE UPDATES: 5 NOV 2000 HIGHEST RN 301296-06-0

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L41 96 S E143-238

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2 RN **168172-57-4** REGISTRY
3 RN **168172-56-3** REGISTRY
4 RN **168172-24-5** REGISTRY
5 RN **158999-67-8** REGISTRY
6 RN **158894-26-9** REGISTRY
7 RN **158894-25-8** REGISTRY
8 RN **158894-24-7** REGISTRY
9 RN **145631-95-4** REGISTRY
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12 RN **142695-69-0** REGISTRY
13 RN **142695-68-9** REGISTRY
14 RN **142695-67-8** REGISTRY
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17 RN **142589-96-6** REGISTRY
18 RN **142589-95-5** REGISTRY
19 RN **142589-94-4** REGISTRY
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35 RN **140385-90-6** REGISTRY
36 RN **140385-89-3** REGISTRY
37 RN **140385-88-2** REGISTRY
38 RN **140210-94-2** REGISTRY
39 RN **140210-93-1** REGISTRY
40 RN **140210-92-0** REGISTRY
41 RN **140210-91-9** REGISTRY

42 RN **140210-90-8** REGISTRY
43 RN **140210-89-5** REGISTRY
44 RN **140210-88-4** REGISTRY
45 RN **140210-87-3** REGISTRY
46 RN **140210-86-2** REGISTRY
47 RN **140210-85-1** REGISTRY
48 RN **140197-06-4** REGISTRY
49 RN **140197-05-3** REGISTRY
50 RN **140197-04-2** REGISTRY
51 RN **140197-03-1** REGISTRY
52 RN **140197-02-0** REGISTRY
53 RN **140197-01-9** REGISTRY
54 RN **140197-00-8** REGISTRY
55 RN **140196-99-2** REGISTRY
56 RN **140196-98-1** REGISTRY
57 RN **140196-97-0** REGISTRY
58 RN **140196-96-9** REGISTRY
59 RN **140196-95-8** REGISTRY
60 RN **140196-94-7** REGISTRY
61 RN **140196-93-6** REGISTRY
62 RN **140196-92-5** REGISTRY
63 RN **140196-91-4** REGISTRY
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66 RN **140196-87-8** REGISTRY
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68 RN **140196-83-4** REGISTRY
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73 RN **140196-78-7** REGISTRY
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76 RN **140196-75-4** REGISTRY
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79 RN **140196-72-1** REGISTRY
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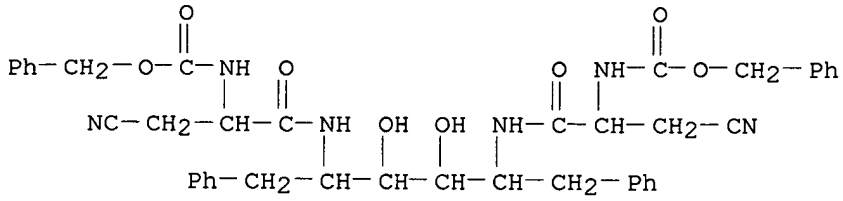
81 RN **140196-70-9** REGISTRY
82 RN **140196-69-6** REGISTRY
83 RN **140196-68-5** REGISTRY
84 RN **140196-67-4** REGISTRY
85 RN **140196-66-3** REGISTRY
86 RN **140196-65-2** REGISTRY
87 RN **140196-64-1** REGISTRY
88 RN **140196-62-9** REGISTRY
89 RN **140196-60-7** REGISTRY
90 RN **140196-55-0** REGISTRY
91 RN **137755-25-0** REGISTRY
DR 163451-79-4, 188674-00-2
92 RN **134878-17-4** REGISTRY
93 RN **134805-67-7** REGISTRY
94 RN **134805-65-5** REGISTRY
95 RN **134805-64-4** REGISTRY
96 RN **129467-48-7** REGISTRY
DR 142861-15-2

=> d ide can 1 10 20 30 40 50 60 70 80 90 96

L41 ANSWER 1 OF 96 REGISTRY COPYRIGHT 2000 ACS
RN **168172-58-5** REGISTRY

CN 2,5,10,13-Tetraazatetradecanedioic acid, 3,12-bis(cyanomethyl)-7,8-dihydroxy-4,11-dioxo-6,9-bis(phenylmethyl)-, bis(phenylmethyl) ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C42 H44 N6 O8
SR CA
LC STN Files: CA, CAPLUS

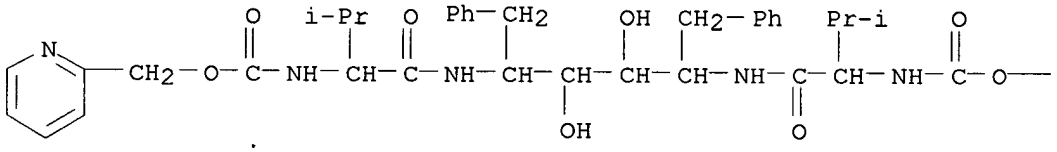


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 123:218429

L41 ANSWER 10 OF 96 REGISTRY COPYRIGHT 2000 ACS
RN **144239-46-3** REGISTRY
CN Hexitol, 1,2,5,6-tetradeoxy-2,5-bis[[3-methyl-1-oxo-2-[[(2-pyridinylmethoxy)carbonyl]amino]butyl]amino]-1,6-diphenyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C42 H52 N6 O8
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

PAGE 1-A



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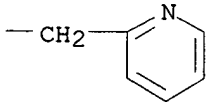


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

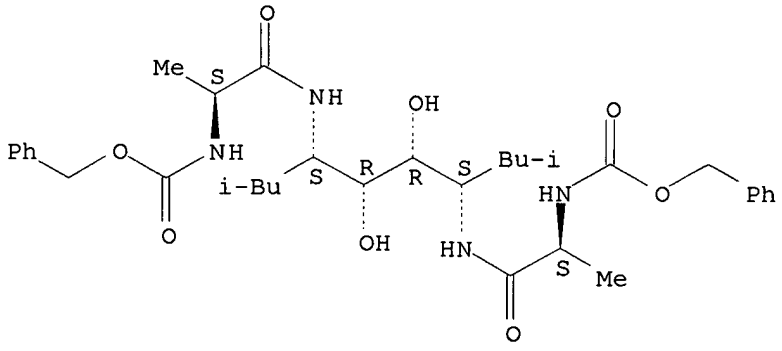
REFERENCE 1: 123:218429

REFERENCE 2: 118:192283

L41 ANSWER 20 OF 96 REGISTRY COPYRIGHT 2000 ACS
RN **142285-41-4** REGISTRY
CN 2,5,10,13-Tetraazatetradecanedioic acid, 7,8-dihydroxy-3,12-dimethyl-6,9-bis(2-methylpropyl)-4,11-dioxo-, bis(phenylmethyl) ester,

[3S-(3R*,6R*,7S*,8S*,9R*,12R*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
DR 142285-37-8
MF C34 H50 N4 O8
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



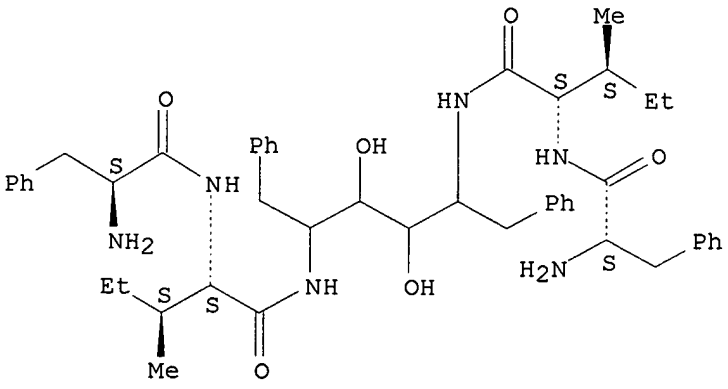
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 119:85387

REFERENCE 2: 118:234482

L41 ANSWER 30 OF 96 REGISTRY COPYRIGHT 2000 ACS
RN **140386-98-7** REGISTRY
CN Hexitol, 1,2,5,6-tetradeoxy-1,6-diphenyl-2,5-bis[(N-L-phenylalanyl-L-isoleucyl)amino]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Isoleucinamide, L-phenylalanyl-, hexitol deriv.
FS STEREOSEARCH
MF C48 H64 N6 O6
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



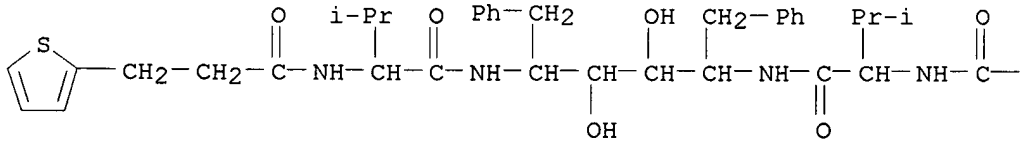
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 121:301325

REFERENCE 2: 116:194884

L41 ANSWER 40 OF 96 REGISTRY COPYRIGHT 2000 ACS
RN **140210-92-0** REGISTRY
CN Hexitol, 1,2,5,6-tetradeoxy-2,5-bis[[3-methyl-1-oxo-2-[[1-oxo-3-(2-thienyl)propyl]amino]butyl]amino]-1,6-diphenyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C42 H54 N4 O6 S2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

PAGE 1-A



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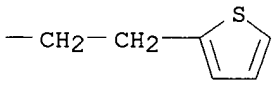
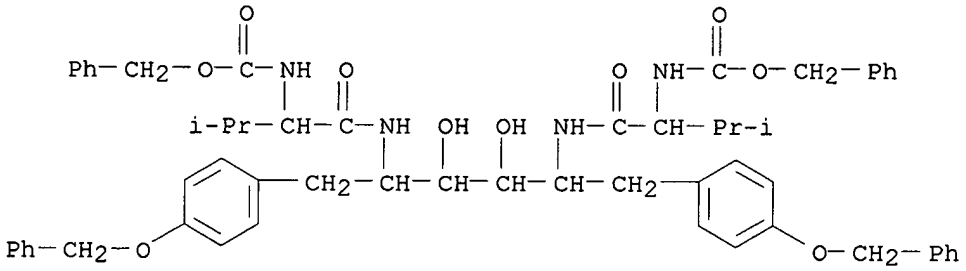


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 121:301325

REFERENCE 2: 116:194884

L41 ANSWER 50 OF 96 REGISTRY COPYRIGHT 2000 ACS
RN **140197-04-2** REGISTRY
CN 2,5,10,13-Tetraazatetradecanedioic acid, 7,8-dihydroxy-3,12-bis(1-methylethyl)-4,11-dioxo-6,9-bis[[4-(phenylmethoxy)phenyl]methyl]-, bis(phenylmethyl) ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C58 H66 N4 O10
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

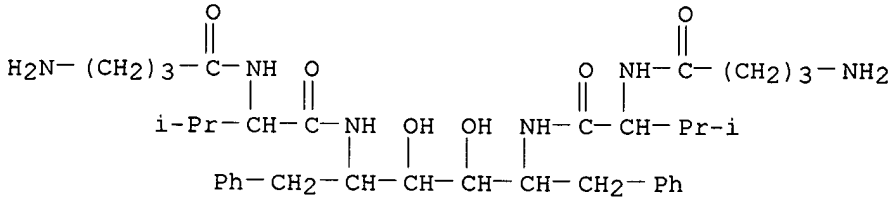


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 121:301325

REFERENCE 2: 116:194884

L41 ANSWER 60 OF 96 REGISTRY COPYRIGHT 2000 ACS
RN **140196-94-7** REGISTRY
CN Butanamide, N,N'-[2,3-dihydroxy-1,4-bis(phenylmethyl)-1,4-butanediyl]bis[2-[(4-amino-1-oxobutyl)amino]-3-methyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C36 H56 N6 O6
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

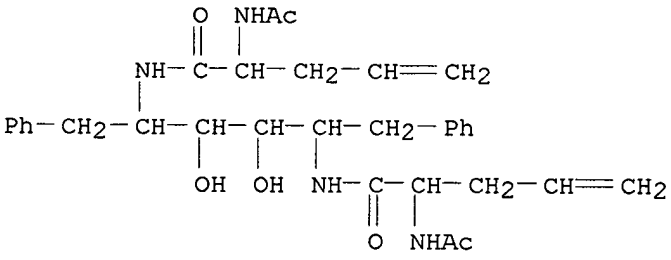


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 121:301325

REFERENCE 2: 116:194884

L41 ANSWER 70 OF 96 REGISTRY COPYRIGHT 2000 ACS
RN **140196-81-2** REGISTRY
CN 4-Pentenamide, N,N'-[2,3-dihydroxy-1,4-bis(phenylmethyl)-1,4-butanediyl]bis[2-(acetylamino)- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C32 H42 N4 O6
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



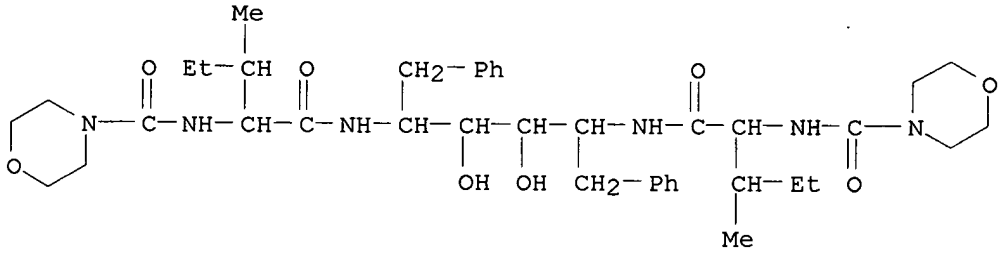
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 121:301325

REFERENCE 2: 116:194884

L41 ANSWER 80 OF 96 REGISTRY COPYRIGHT 2000 ACS
RN **140196-71-0** REGISTRY
CN 4-Morpholinecarboxamide, N,N'-[[2,3-dihydroxy-1,4-bis(phenylmethyl)-1,4-butanediyl]bis[imino[1-(1-methylpropyl)-2-oxo-2,1-ethanediyl]]]bis- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C40 H60 N6 O8

SR CA
LC STN Files: CA, CAPLUS, USPATFULL



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

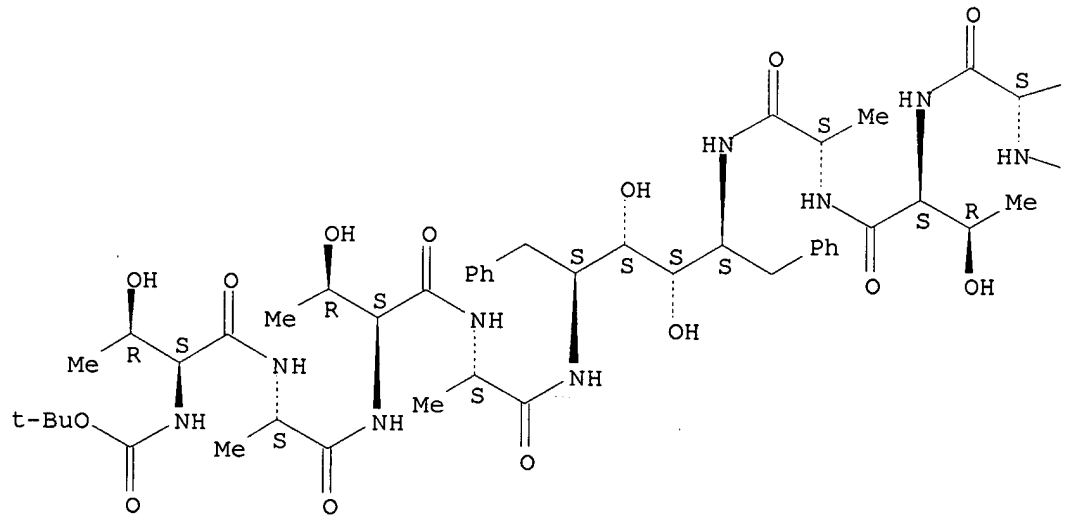
REFERENCE 1: 121:301325

REFERENCE 2: 116:194884

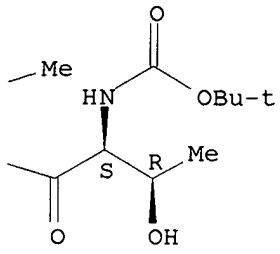
L41 ANSWER 90 OF 96 REGISTRY COPYRIGHT 2000 ACS
RN **140196-55-0** REGISTRY
CN L-Mannitol, 1,2,5,6-tetradeoxy-2,5-bis[[N-[N-[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-threonyl]-L-alanyl]-L-threonyl]-L-alanyl]amino]-1,6-diphenyl- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C56 H88 N10 O18
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



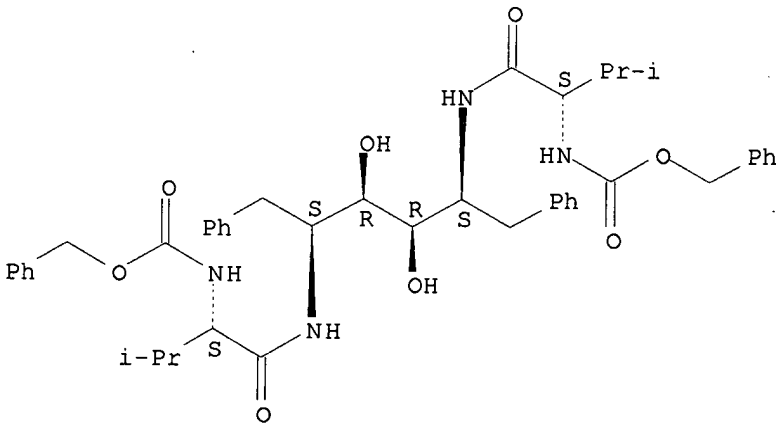
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 121:301325

REFERENCE 2: 116:194884

L41 ANSWER 96 OF 96 REGISTRY COPYRIGHT 2000 ACS
RN **129467-48-7** REGISTRY
CN L-Iditol, 1,2,5,6-tetradeoxy-2,5-bis[[(2S)-3-methyl-1-oxo-2-[[(phenylmethoxy)carbonyl]amino]butyl]amino]-1,6-diphenyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Iditol, 1,2,5,6-tetradeoxy-2,5-bis[[3-methyl-1-oxo-2-[[(phenylmethoxy)carbonyl]amino]butyl]amino]-1,6-diphenyl-, [2(S),5(S)]-
OTHER NAMES:
CN A 75925
FS STEREOSEARCH
DR 142861-15-2
MF C44 H54 N4 O8
SR CA
LC STN Files: AIDSLINE, BEILSTEIN*, BIOSIS, CA, CAPLUS, CASREACT, CHEMINFORMRX, DDFU, DRUGU, MEDLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



19 REFERENCES IN FILE CA (1967 TO DATE)
19 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:45104

REFERENCE 2: 130:276229

REFERENCE 3: 128:238962

REFERENCE 4: 128:30075

REFERENCE 5: 127:75549

REFERENCE 6: 124:344059

REFERENCE 7: 121:205978

REFERENCE 8: 119:139718

REFERENCE 9: 119:138493

REFERENCE 10: 119:85387

=> file reg

FILE 'REGISTRY' ENTERED AT 12:27:30 ON 06 NOV 2000
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DICTIONARY FILE UPDATES: 5 NOV 2000 HIGHEST RN 301296-06-0

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FILE COVERS 1967 - 6 Nov 2000 VOL 133 ISS 20
FILE LAST UPDATED: 5 Nov 2000 (20001105/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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Now you can extend your author, patent assignee, patent information, and title searches back to 1907. The records from 1907-1966 now have this searchable data in CAOLD. You now have electronic access to all of CA: 1907 to 1966 in CAOLD and 1967 to the present in CAPLUS on STN.

Searched by Edward Hart 305-9203

=> d stat que l44 nos

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L7              STR
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L40           10 SEA FILE=CAPLUS ABB=ON  PLU=ON  L39 AND PATENT/DT
L44            6 SEA FILE=CAPLUS ABB=ON  PLU=ON  L30 NOT (L33 OR L37 OR (2000
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=> d ibib abs hitrn l44 tot

L44 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:215813 CAPLUS
DOCUMENT NUMBER: 126:303001
TITLE: Development and Standardization of an Immuno-Quantified Solid Phase Assay for HIV-1 Aspartyl Protease Activity and Its Application to the Evaluation of Inhibitors
AUTHOR(S): Fournout, S.; Roquet, F.; Salhi, S. L.; Seyer, R.; Valverde, V.; Masson, J. M.; Jouin, P.; Pau, B.; Nicolas, M.; Hanin, V.
CORPORATE SOURCE: Laboratoire d'Immunoanalyse et Innovation en Biologie Clinique, Faculte de Pharmacie, Montpellier, 34060, Fr.
SOURCE: Anal. Chem. (1997), 69(9), 1746-1752
CODEN: ANCHAM; ISSN: 0003-2700
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The catELISA technique was modified and standardized for measuring HIV-1 aspartyl protease activity and evaluating the potency of synthetic peptide inhibitors. This immuno-quantified solid phase assay combines the use of an immobilized C-terminal biotinylated peptide as substrate, a crude enzyme prepn., and a highly specific antiserum elicited against the C-terminal product of the enzyme reaction. A std. curve of this C-terminal product was constructed to det. the enzyme activity. This assay, which requires less enzyme and substrate, is more sensitive than the conventional HPLC method. The amts. of C-terminal peptide produced in

soln. as detd. from ELISA and HPLC std. curves were comparable. Analogs of peptidomimetics designed in our lab. were assayed for their potency to inhibit the enzyme. One of them, H4, which is a hydroxyethylamine isostere of the Phe-Pro peptide bond, was a powerful inhibitor.

IT **159552-64-4**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(development and standardization of an immuno-quantified solid phase assay for HIV-1 aspartyl protease activity and its application to the evaluation of inhibitors)

L44 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:623496 CAPLUS
DOCUMENT NUMBER: 123:28607
TITLE: Analogs of cleavage sites as inhibitors of the proteolytic processing of the gag-pol polyprotein of HIV-1
INVENTOR(S): Lindhofer, Horst; Nitschko, Hans; Helm, Klaus
PATENT ASSIGNEE(S): Germany
SOURCE: Ger. Offen., 10 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4332395	A1	19950413	DE 1993-4332395	19930923

AB Peptide analogs of the cleavage sites recognized in the proteolytic processing of the gag-pol polyprotein of human immunodeficiency virus 1 are described for use as inhibitors of viral propagation. The use of the inhibitors in animal cell culture led to the accumulation of a novel 114 kDa processing intermediate.

IT **163967-21-3**
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(proteinase inhibitor; analogs of cleavage sites as inhibitors of proteolytic processing of gag-pol polyprotein of HIV-1)

L44 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:36218 CAPLUS
DOCUMENT NUMBER: 122:4280
TITLE: Characterization of a monoclonal antibody produced in an attempt to mimic the active site of HIV aspartyl protease using haptens based on inhibitor models
AUTHOR(S): Hanin, Veronique; Campagne, Jean-Marc; Dominice, Carole; Mani, Jean-Claude; Dufour, Marie-Noeelle; Jouin, Patrick; Pau, Bernard
CORPORATE SOURCE: Immunoanalyse et Innovation en Biologie Clinique, CNRS UMR 9921, Faculte de Pharmacie, 15 Avenue Charles Flahault, Montpellier, 34060/1, Fr.
SOURCE: J. Immunol. Methods (1994), 173(2), 139-47
CODEN: JIMMBG; ISSN: 0022-1759
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The high binding affinity and specificity of antibodies for a great variety of ligands has been widely exploited in structure-activity relation studies of biomols. and more recently in the development of new catalysts for several chem. reactions. It is assumed that antibodies generated against haptenic protease inhibitors would recognize both these haptens and the substrate of the model proteolytic reaction. The authors have produced antibodies against HIV PRp12 aspartyl protease substrate analogs, chem. modified at the scissile bond, Phe-Pro. Identical chem.

modifications have been reported for related HIV protease inhibitors. The authors finally selected an anti-hapten monoclonal antibody that specifically recognized the substrate and those haptens with both the phenylalanyl side chain and the prolyl pyrrolidine ring. This selectivity of recognition suggests that such an antibody might mimic the catalytic site of the model protease.

IT **159552-64-4**
RL: BIOL (Biological study)
(monoclonal antibodies to, as mimics to HIV aspartyl protease)

L44 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:289408 CAPLUS
DOCUMENT NUMBER: 120:289408
TITLE: Three-dimensional QSAR of human immunodeficiency virus (I) protease inhibitors. 1. A CoMFA study employing experimentally-determined alignment rules
AUTHOR(S): Waller, Chris L.; Oprea, Tudor I.; Giolitti, Alessandro; Marshall, Garland R.
CORPORATE SOURCE: Cent. Mol. Des., Washington Univ., St. Louis, MO, 63130, USA
SOURCE: J. Med. Chem. (1993), 36(26), 4152-60
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Comparative mol. field anal. (CoMFA), a 3-dimensional, quant. structure-activity relationship (QSAR) paradigm, was used to exam. the correlations between the calcd. physicochem. properties and in the vitro activities of a series of human immunodeficiency virus (HIV-1) protease inhibitors. The training set consisted of 59 mols. from five structurally-diverse transition-state isostere classes: hydroxyethylamine, statine, norstatine, keto amide, and dihydroxyethylene. The availability of x-ray crystallog. data for at least one representative from each class bound to the protease provided information regarding not only the active conformation of each ligand but also, via superimposition of protease backbones, the relative positions of each ligand with respect to one another in the active site of the enzyme. Once aligned, these mols. served as templates on which addnl. congeners were field-fit minimized. Addnl. alignment rules were derived from minimization of the ligands in the active site of the semirigid protease. The predictive ability of each resultant model was evaluated using a test set comprised of mols. contg. a novel transition-state isostere: hydroxyethylurea. Crystallog. studies indicated an unexpected binding mode for this series of compds. which precluded the use of the field-fit minimization alignment technique. The test set mols. were, therefore, subjected to a limited systematic search in conjunction with active-site minimization. The conformer of each mol. expressing the lowest interaction energy with the active site was included in the test set. Field-fit minimization of neutral mols. to crystal ligands and active-site minimizations of protonated ligands yielded predictive correlations for HIV-1 protease inhibitors. The use of crystallog. data in the detn. of alignment rules and field-fit minimization as a mol. alignment tool in the absence of direct exptl. data regarding binding modes is strongly supported by these results.

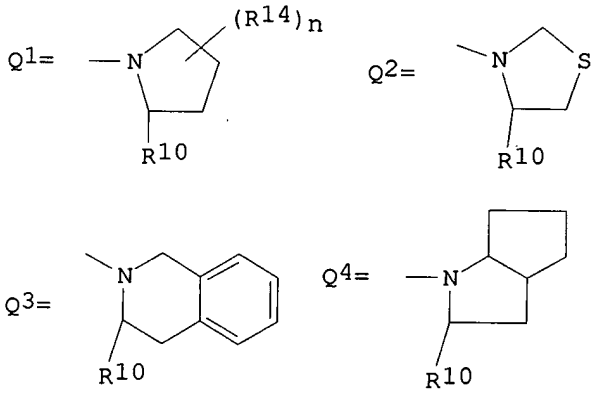
IT **141171-74-6 141171-78-0**
RL: BIOL (Biological study)
(human immunodeficiency virus 1 protease inhibition by, QSAR of)

L44 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:245776 CAPLUS
DOCUMENT NUMBER: 120:245776
TITLE: Preparation of cyclic amides of 3-amino-2-hydroxycarboxylic acids as HIV protease inhibitors
INVENTOR(S): Krantz, Alexander; Tam, Tim Fat; Castelhano, Arlindo Lucas; Nestor, John Joseph, Jr.
PATENT ASSIGNEE(S): Syntex (U.S.A.), Inc., USA

SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9313066	A1	19930708	WO 1992-US10772	19921218
W: AU, CA, FI, HU, JP, KR, NO, NZ				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9332782	A1	19930728	AU 1993-32782	19921218
ZA 9209869	A	19940620	ZA 1992-9869	19921218
PRIORITY APPLN. INFO.:			US 1991-812905	19911220
			WO 1992-US10772	19921218

OTHER SOURCE(S): MARPAT 120:245776
GI



AB R1R2NCHR3CONHCHR4CR5R6COR7 [R1 = (ar)alkoxycarbonyl, (substituted) aralkanoyl, aroyl, heterocyclylcarbonyl, aryloxyalkanoyl, carbamoyl, heterocyclyloxyalkanoyl; R2, R5 = H; R3 = (substituted) alkyl, R4 = (substituted) aryl, aralkyl; R6 = OH; R5R6 = O; R1 = Q1-Q4, etc.; n = 0-2; R10 = alkoxycarbonyl, (substituted) carbamoyl; R14 = OH, alkyl, alkoxy, Ph], were prepd. Thus, N'-tert-Bu prolinamide (prepn. given) was coupled with (2S,3S)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoic acid using EDCI/hydroxybenzotriazole in DMF to give 1-[(2S,3S)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-N'-tert-butyl-L-prolinamide. I inhibited HIV protease with IC50 = 0.49-30 nM. I dosage formulations are given.

IT **141171-74-6P 141171-78-0P 153290-16-5P**
153290-17-6P 153290-18-7P 153290-23-4P
153290-26-7P 153290-35-8P 153290-37-0P
153290-38-1P 153290-41-6P 153290-42-7P
153290-43-8P 153290-51-8P 153290-52-9P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of, as HIV protease inhibitor)

IT **153291-06-6P 153291-08-8P 153291-09-9P**
153291-24-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as intermediate for HIV protease inhibitor)

L44 ANSWER 6 OF 6 CAPLUS

ACCESSION NUMBER: 1992:227702 CAPLUS
DOCUMENT NUMBER: 116:227702
TITLE: Intriguing structure-activity relations underlie the potent inhibition of HIV protease by norstatine-based peptides
AUTHOR(S): Tam, Tim F.; Carriere, Julie; MacDonald, I. David; Castelhano, Arlindo L.; Pliura, Diana H.; Dewdney, Nolan J.; Thomas, Everton M.; Bach, Chinh; Barnett, Jimmy; et al.
CORPORATE SOURCE: Syntex Res. Canada, Mississauga, ON, L5N 3X4, Can.
SOURCE: J. Med. Chem. (1992), 35(7), 1318-20
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Phenylnorstatine contg. peptides extending from the P2 to P1' positions, with L-proline at the P1' position and S-stereochem. of the P1 component, exhibit impressive potency vs. HIV-1 potease (IC50 = 0.58-7.4 nM). Representative ketoamides are also active with slightly lower potency. Analogous hydroxyethylamines have previously been reported to be potent inhibitors of this enzyme. The presence of an addnl. carbonyl in this series of proline-based inhibitors enhances their potency, and alters structure-activity relations profoundly. Whereas divergent effects on potency have been obsd. for epimeric hydroxyethylamines upon extension of such P1' terminal peptides to P3' with Ile-Val, lengthening of norstatine contg.-inhibitors in the same fashion, dramatically increases the potency of the R-diastereomer and leaves the IC50 of the S-epimer essentially unchanged. Most interestingly, amino acid residues in the P1' position contg. parent and fused piperidines lower activity in the norstatine series. By contrast, significant enhancements in inhibitor potency were reported in the hydroxyethylamine series for such proline replacements. Conformational preferences of 6 member rings influenced by A1,3-strain may contribute to the redn. in potency obsd. for the norstatine contg. peptides.

IT **141171-74-6 141171-78-0**
RL: BIOL (Biological study)
(human immunodeficiency virus 1 protease inhibition by)

=> set hitrn 1-6

HITRN 1-6 IS NOT A VALID SET OPTION
For an explanation of the SET command, enter HELP SET at an arrow prompt (=>).

=> set hit rn 1-6

HIT RN 1-6 IS NOT A VALID SET OPTION
For an explanation of the SET command, enter HELP SET at an arrow prompt (=>).

=> sel hit rn 1-6

E239 THROUGH E259 ASSIGNED

=> file reg

FILE 'REGISTRY' ENTERED AT 12:31:54 ON 06 NOV 2000
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STRUCTURE FILE UPDATES: 5 NOV 2000 HIGHEST RN 301296-06-0
DICTIONARY FILE UPDATES: 5 NOV 2000 HIGHEST RN 301296-06-0

TSCA INFORMATION NOW CURRENT THROUGH July 8, 2000

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=> d his l45

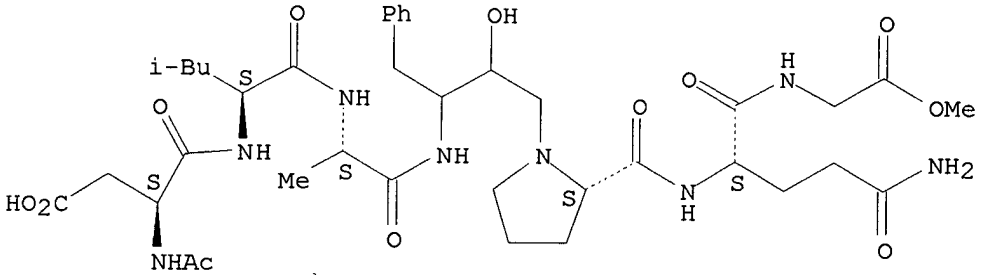
(FILE 'CAPLUS' ENTERED AT 12:30:32 ON 06 NOV 2000)
SEL HIT RN 1-6

FILE 'REGISTRY' ENTERED AT 12:31:54 ON 06 NOV 2000
L45 21 S E239-259

=> d ide can 1 5 10 15 20 21 l45

L45 ANSWER 1 OF 21 REGISTRY COPYRIGHT 2000 ACS
RN **163967-21-3** REGISTRY
CN Glycine, N-[N2-[1-[3-[[N-[N-(N-acetyl-L-.alpha.-aspartyl)-L-leucyl]-L-alanyl]amino]-2-hydroxy-4-phenylbutyl]-L-prolyl]-L-glutaminyl]-, 1-methyl ester (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C38 H58 N8 O12
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

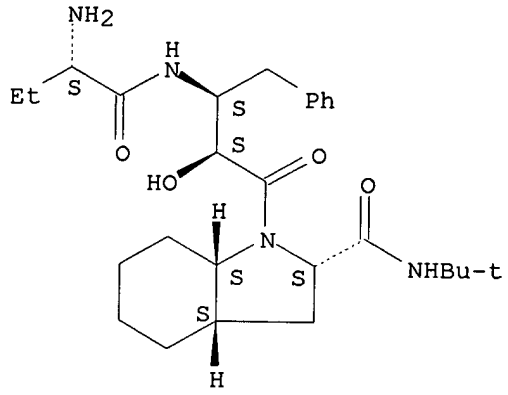


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 123:28607

L45 ANSWER 5 OF 21 REGISTRY COPYRIGHT 2000 ACS
RN **153291-08-8** REGISTRY
CN 1H-Indole-2-carboxamide, 1-[3-[(2-amino-1-oxobutyl)amino]-2-hydroxy-1-oxo-4-phenylbutyl]-N-(1,1-dimethylethyl)octahydro-, [2S-[1[2R*,3R*(R*)],2.alpha.,3a.beta.,7a.beta.]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H42 N4 O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

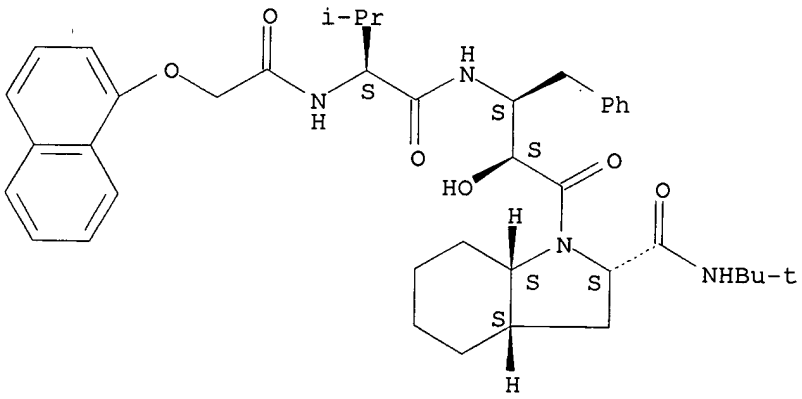


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 120:245776

L45 ANSWER 10 OF 21 REGISTRY COPYRIGHT 2000 ACS
RN **153290-42-7** REGISTRY
CN 1H-Indole-2-carboxamide, N-(1,1-dimethylethyl)octahydro-1-[2-hydroxy-3-[[3-methyl-2-[[(1-naphthalenyloxy)acetyl]amino]-1-oxobutyl]amino]-1-oxo-4-phenylbutyl]-, [2S-[1[2R*,3R*(R*)],2.alpha.,3a.beta.,7a.beta.]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C40 H52 N4 O6
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



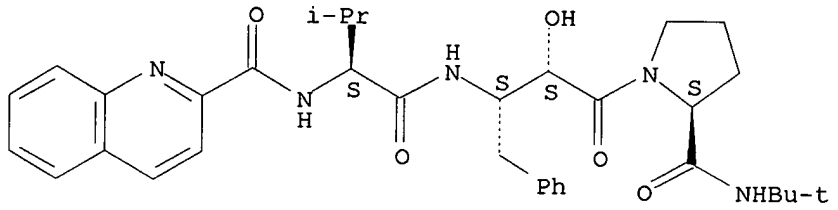
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 120:245776

L45 ANSWER 15 OF 21 REGISTRY COPYRIGHT 2000 ACS
RN **153290-26-7** REGISTRY
CN 2-Quinolinecarboxamide, N-[1-[[[3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2-hydroxy-3-oxo-1-(phenylmethyl)propyl]amino]carbonyl]-2-methylpropyl]-, [2S-[1[1R*(R*),2R*],2R*]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C34 H43 N5 O5
SR CA

LC STN Files: CA, CAPLUS

Absolute stereochemistry.

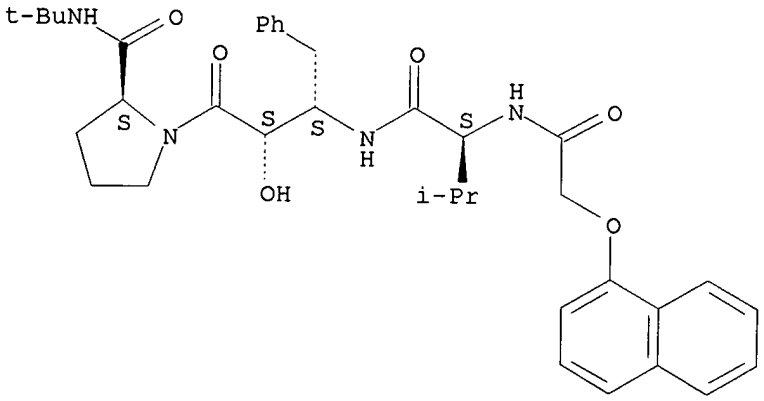


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 120:245776

L45 ANSWER 20 OF 21 REGISTRY COPYRIGHT 2000 ACS
RN **141171-78-0** REGISTRY
CN 2-Pyrrolidinecarboxamide, N-(1,1-dimethylethyl)-1-[2-hydroxy-3-[[3-methyl-2-[[(1-naphthalenyloxy)acetyl]amino]-1-oxobutyl]amino]-1-oxo-4-phenylbutyl]-, [2S-[1[2R*,3R*(R*)],2R*]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C36 H46 N4 O6
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, TOXLIT
(*File contains numerically searchable property data)

Absolute stereochemistry.



3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 120:289408

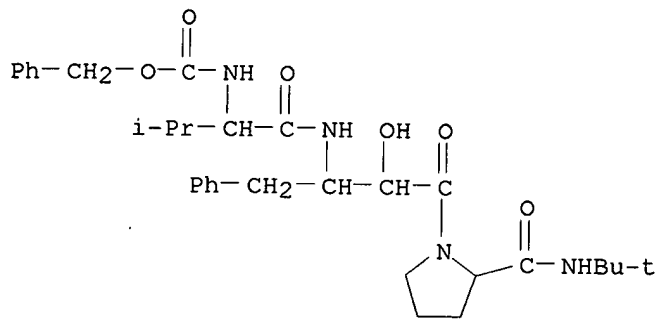
REFERENCE 2: 120:245776

REFERENCE 3: 116:227702

L45 ANSWER 21 OF 21 REGISTRY COPYRIGHT 2000 ACS
RN **141171-74-6** REGISTRY
CN Carbamic acid, [1-[[[3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2-hydroxy-3-oxo-1-(phenylmethyl)propyl]amino]carbonyl]-2-methylpropyl]-, phenylmethyl ester, [2S-[1[2R*,3R*(R*)],2R*]]- (9CI) (CA INDEX NAME)
MF C32 H44 N4 O6
SR CA

Searched by Edward Hart 305-9203

LC STN Files: BEILSTEIN*, CA, CAPLUS, TOXLIT
(*File contains numerically searchable property data)



3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 120:289408

REFERENCE 2: 120:245776

REFERENCE 3: 116:227702

=> file caplus

FILE 'CAPLUS' ENTERED AT 12:34:59 ON 06 NOV 2000
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1967 - 6 Nov 2000 VOL 133 ISS 20
FILE LAST UPDATED: 5 Nov 2000 (20001105/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

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=> d stat que l47 nos

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L5		STR
L7		STR
L11		STR
L15		STR
L17		STR
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Searched by Edward Hart 305-9203

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L32         439 SEA FILE=CAPLUS ABB=ON  PLU=ON  L26
L33           2 SEA FILE=CAPLUS ABB=ON  PLU=ON  L27 AND L28 AND L29 AND L30
                AND L31 AND L32
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L37          19 SEA FILE=CAPLUS ABB=ON  PLU=ON  L36 NOT (2000 OR 1999 OR
                1998)/PY
L39          68 SEA FILE=CAPLUS ABB=ON  PLU=ON  L29 NOT (L33 OR L37 OR (2000
                OR 1999 OR 1998)/PY)
L40          10 SEA FILE=CAPLUS ABB=ON  PLU=ON  L39 AND PATENT/DT
L44           6 SEA FILE=CAPLUS ABB=ON  PLU=ON  L30 NOT (L33 OR L37 OR (2000
                OR 1999 OR 1998)/PY OR L40)
L46         280 SEA FILE=CAPLUS ABB=ON  PLU=ON  L31 AND L32
L47          29 SEA FILE=CAPLUS ABB=ON  PLU=ON  L46 NOT (L33 OR L37 OR (2000
                OR 1999 OR 1998)/PY OR L40 OR L44)
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=> d ibib abs hitrn 147 tot

L47 ANSWER 1 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:222335 CAPLUS
DOCUMENT NUMBER: 128:278678
TITLE: Inhibitors of the HIV protease for therapy of AIDS -current status and future prospects
AUTHOR(S): Korant, Bruce D.
CORPORATE SOURCE: Virus Laboratory, Molecular Biology Department, DuPont Merck Pharmaceutical Co., Wilmington, DE, 19880-0336, USA
SOURCE: Biomed. Health Res. (1997), 15(Medical Aspects of Proteases and Protease Inhibitors), 113-117
CODEN: BIHREN; ISSN: 0929-6743
PUBLISHER: IOS Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB New, potent therapies for HIV disease are becoming available, based on design of synthetic inhibitor of the viral protease, an essential viral enzyme. The results in clin. trials have been impressive with most treated individuals benefiting in terms of reduced quantity of detectable virus, enhanced nos. of CD4 lymphocytes and improvements in quality and duration of life. There are some anecdotal accounts of individual cures (unpublished at present). However, there are some remaining negatives assocd. with the new drugs, including cost, side effects and appearance of drug-resistant strains of HIV. Problems and future prospects for use of protease inhibitors in AIDS are discussed.

IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors of the HIV protease for therapy of AIDS -current status and future prospects)

L47 ANSWER 2 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:15429 CAPLUS
DOCUMENT NUMBER: 128:175813

Searched by Edward Hart 305-9203

TITLE: HIV protease inhibitors, saquinavir, indinavir and ritonavir: inhibition of CYP3A4-mediated metabolism of testosterone and benzoxazinorifamycin, KRM-1648, in human liver microsomes
AUTHOR(S): Inaba, T.; Fischer, N. E.; Riddick, D. S.; Stewart, D. J.; Hidaka, T.
CORPORATE SOURCE: Faculty of Medicine, Department of Pharmacology, University of Toronto, Toronto M5S1A8, Can.
SOURCE: Toxicol. Lett. (1997), 93(2,3), 215-219
CODEN: TOLED5; ISSN: 0378-4274
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The protease inhibitors, ritonavir, indinavir and saquinavir, the most potent anti-HIV drugs developed to date, interact with many drugs by competing for CYP3A4, an enzyme central to the metab. of a wide variety of compds. Human liver microsomes were used to compare inhibition by these three protease inhibitors. The inhibition was the greatest with ritonavir and indinavir and less potent with saquinavir.

IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(HIV protease inhibitors (saquinavir and indinavir and ritonavir) and inhibition of cytochrome P 450 3A4-mediated metab. of testosterone and benzoxazinorifamycin (KRM-1648) in human liver microsomes)

L47 ANSWER 3 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:792549 CAPLUS
DOCUMENT NUMBER: 128:110427
TITLE: Presence of an inducible HIV-1 latent reservoir during highly active antiretroviral therapy
AUTHOR(S): Chun, Tae-Wook; Stuyver, Lieven; Mizell, Stephanie B.; Ehler, Linda A.; Mican, Jo Ann M.; Baseler, Michael; Lloyd, Alun L.; Nowak, Martin A.; Fauci, Anthony S.
CORPORATE SOURCE: Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1997), 94(24), 13193-13197
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Although highly active antiretroviral therapy (HAART) in the form of triple combinations of drugs including protease inhibitors can reduce the plasma viral load of some HIV-1-infected individuals to undetectable levels, it is unclear what the effects of these regimens are on latently infected CD4+ T cells and what role these cells play in the persistence of HIV-1 infection in individuals receiving such treatment. The present study demonstrates that highly purified CD4+ T cells from 13 of 13 patients receiving HAART with an av. treatment time of 10 mo and with undetectable (<500 copies HIV RNA/mL) plasma viremia by a commonly used bDNA assay carried integrated proviral DNA and were capable of producing infectious virus upon cellular activation in vitro. Phenotypic anal. of HIV-1 produced by activation of latently infected CD4+ T cells revealed the presence in some patients of syncytium-inducing virus. In addn., the presence of unintegrated HIV-1 DNA in infected resting CD4+ T cells from patients receiving HAART, even those with undetectable plasma viremia, suggests persistent active virus replication in vivo.

IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(presence of inducible HIV-1 latent reservoir in CD4+ T cells during highly active antiretroviral therapy in humans)

L47 ANSWER 4 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:792109 CAPLUS
DOCUMENT NUMBER: 128:84166
TITLE: Virological treatment failure of protease inhibitor therapy in an unselected cohort of HIV-infected patients
AUTHOR(S): Fatkenheuer, Gerd; Theisen, Albert; Rockstroh, Jurgen; Grabow, Tanja; Wicke, Christian; Becker, Katja; Wieland, Ulrike; Pfister, Herbert; Reiser, Marcel; Hegener, Petra; Franzen, Caspar; Schwenk, Achim; Salzberger, Bernd
CORPORATE SOURCE: Department of Internal Medicine I, University of Cologne, Cologne, Germany
SOURCE: AIDS (London) (1997), 11(14), F113-F116
CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Our objective was to det. the rate of virol. treatment failure with protease inhibitor therapy in unselected patients and to assess underlying risk factors. Retrospective study in two German tertiary care treatment centers. A total of 198 HIV-infected patients treated with protease inhibitors in 1996. Levels of HIV RNA 1-6 mo after start of treatment; definition of treatment failure of < 1 log10 redn. in plasma HIV RNA within 6 mo after starting protease inhibitor therapy; multivariate anal. of risk factors for treatment failures. A total of 226 treatment episodes with protease inhibitors were evaluable (saquinavir, 83; ritonavir, 47; indinavir, 96). The rate of virol. treatment failure was 44% (saquinavir, 64%; ritonavir, 38%; indinavir, 30%). In a multivariate anal., the following independent risk factors for virol. failure were found: CD4 cell count, pretreatment with antiretroviral drugs (no.), and protease inhibitor (compd.). The relative risk redn. for each CD4 cell count increase was 0.997 (P = 0.012), 2.64 for pretreatment with one or two drugs vs. no drug (P = 0.05), 2.97 for pretreatment with more than two drugs vs. no drug (P = 0.05), and 4.62 for treatment with saquinavir vs. indinavir (P = 0.001). An unexpectedly high rate of virol. treatment failure of protease inhibitor therapy was found in an unselected cohort of HIV-infected patients. Response to antiretroviral combination therapy in normal clin. practice may considerably differ from results of randomized clin. trials. Further studies are warranted to find optimal treatment strategies for both initial and salvage therapy.
IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(virol. treatment failure of protease inhibitor therapy in an unselected cohort of HIV-infected humans)

L47 ANSWER 5 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:758718 CAPLUS
DOCUMENT NUMBER: 128:162583
TITLE: Anti-HIV activity of adefovir (PMEA) and PMPA in combination with antiretroviral compounds: in vitro analyses
AUTHOR(S): Mulato, A.S.; Cherrington, J.M.
CORPORATE SOURCE: Gilead Sciences, Lakeside Drive, Foster City, CA 94404, 333, USA
SOURCE: Antiviral Res. (1997), 36(2), 91-97
CODEN: ARSRDR; ISSN: 0166-3542
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Adefovir (PMEA, 9-(2-phosphonomethoxyethyl)adenine), an acyclic nucleoside phosphonate analog is active against retroviruses, hepadnaviruses and

herpesviruses. Adefovir dipivoxil, an orally bioavailable prodrug of adefovir is currently in phase III clin. trials for the treatment of HIV and phase II clin. trials for the treatment of HBV infections. PMPA (9-(2-phosphonomethoxypropyl)adenine) is a related acyclic nucleoside phosphonate analog that has demonstrated potent anti-SIV activity in rhesus macaques and recently has shown marked anti-HIV activity in a phase I clin. study. Since the std. of care for AIDS patients has become combination therapy, the effects of other antiretroviral compds. (d4T, ddC, AZT, ddI, 3TC, nelfinavir, ritonavir, indinavir, and saquinavir) on the anti-HIV activity of adefovir and PMPA were investigated in vitro. Adefovir and PMPA both demonstrated strong synergistic anti-HIV activity in combination with AZT. Adefovir demonstrated minor to moderate synergistic inhibition of HIV replication in combination with PMPA, d4T, ddC, nelfinavir, ritonavir, and saquinavir. PMPA demonstrated minor synergistic inhibition of HIV replication in combination with ddI and nelfinavir (and adefovir). All other combinations showed additive inhibition of HIV replication in vitro. Importantly, no antagonistic interactions were measured for any of the adefovir or PMPA combinations.

IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Anti-HIV activity of adefovir and PMPA in combination with antiretroviral compds.)

L47 ANSWER 6 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:737957 CAPLUS
DOCUMENT NUMBER: 127:341319
TITLE: Therapeutic advances: protease inhibitors for the treatment of HIV-1 infection
AUTHOR(S): Misson, J.; Clark, W.; Kendall, M. J.
CORPORATE SOURCE: Department of Medicines Management, Keele University, Keele, UK
SOURCE: J. Clin. Pharm. Ther. (1997), 22(2), 109-117
CODEN: JCPTED; ISSN: 0269-4727
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 32 refs., describing the 3 most recently introduced protease inhibitors used to treat HIV-1 infection.. Background data are given on HIV infection and the treatment options. Detailed information on ritonavir, saquinavir and indinavir is provided. These new drugs are useful addns. to the therapeutic armamentarium for the treatment of HIV infection. They need to be used under close supervision by specialists.

IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HIV-1 infection of humans treatment by)

L47 ANSWER 7 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:737726 CAPLUS
DOCUMENT NUMBER: 128:43217
TITLE: Current antiretrovirals - a review
AUTHOR(S): Hirsch, Martin S.
CORPORATE SOURCE: Harvard Medical School, Infectious Disease Unit, Massachusetts General Hospital, Boston, MA, USA
SOURCE: Antiviral Ther. (1997), 2(Suppl. 4), 19-40
CODEN: ANTHFA; ISSN: 1359-6535
PUBLISHER: International Medical Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 145 refs.

IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(current antiretrovirals)

L47 ANSWER 8 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:727376 CAPLUS
DOCUMENT NUMBER: 128:30079
TITLE: Nonsymmetrically Substituted Cyclic Urea HIV Protease Inhibitors
AUTHOR(S): Wilkerson, Wendell W.; Dax, Scott; Cheatham, Walter W.
CORPORATE SOURCE: DuPont Merck Pharmaceutical Company, Wilmington, DE, 19880-0500, USA
SOURCE: J. Med. Chem. (1997), 40(25), 4079-4088
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of nonsym. substituted cyclic urea carboxamides was synthesized and evaluated for antiviral activity as a function of the inhibition of HIV-protease. Selected protease inhibitors were also evaluated for oral bioavailability. The synthesis, pharmacol., quant. structure-activity relationship (QSAR), and pharmacokinetics for the series will be discussed.
IT **127779-20-8**, Ro 31-8959 **155213-67-5**, ABT 538
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(prepn. of substituted cyclic ureas as HIV protease inhibitors)

L47 ANSWER 9 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:704700 CAPLUS
DOCUMENT NUMBER: 128:147
TITLE: Protease inhibitor therapy in children with perinatally acquired HIV infection
AUTHOR(S): Rutstein, Richard M.; Feingold, Anat; Meislich, Debrah; Word, Bonnie; Rudy, Bret
CORPORATE SOURCE: Division of General Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, 19104, USA
SOURCE: AIDS (London) (1997), 11(12), F107-F111
CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study reviewed the short-term response and safety of protease inhibitor therapy in HIV-infected children. The design involved a retrospective chart review of open-label protease inhibitor-contg. combination therapy. The setting consisted of two urban pediatric HIV centers. Patients consisted of twenty-eight HIV-infected children were prescribed 30 protease inhibitor-contg. antiretroviral therapy combinations. The median age at initiation of protease inhibitor antiretroviral therapy was 79 mo. Patients had been on previous antiretroviral therapy for a mean of 45.5 mo. Of the 28 children who completed at least 1 mo of therapy, 26 experienced marked virol. and immunol. improvement (mean maximal decrease in viral load 1.90 log10 copies/mL; SD, 0.8; mean maximal rise in CD4+ lymphocytes of 279 .times. 106/l; SD, 300 .times. 106/l). Eleven patients achieved a viral nadir of < 400 copies/mL, and seven sustained this level of viral suppression for a mean of 6 mo. Indinavir use was assocd. with a high incidence of renal side-effects, including two patients who developed interstitial nephritis. Two patients on ritonavir experienced a significant elevation of liver enzymes. Protease inhibitor therapy was assocd. with substantial short-term virol. and immunol. improvement in this primarily heavily pretreated cohort, with 25% maintaining a viral load of < 400 copies/mL after 6 mo of therapy. There was a significant rate of adverse events. Pharmacokinetic and safety data are needed to guide aggressive antiretroviral therapy in HIV-infected children, and further treatment options are required for those failing or intolerant to the available

protease inhibitors.

IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Protease inhibitor treatment of perinatally acquired HIV infection in pediatric humans)

L47 ANSWER 10 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:704698 CAPLUS
DOCUMENT NUMBER: 128:145
TITLE: Toxicity, efficacy, plasma drug concentrations and protease mutations in patients with advanced HIV infection treated with ritonavir plus saquinavir
AUTHOR(S): Lorenzi, Patrizio; Yerly, Sabine; Abderrakim, Karmine; Fathi, Marc; Rutschmann, Olivier T.; Von Overbeck, Jan; Leduc, Dominique; Perrin, Luc; Hirschel, Bernard
CORPORATE SOURCE: The Swiss HIV Cohort Study, Division of Infectious Diseases, University Hospital, Geneva, 1211, Switz.
SOURCE: AIDS (London) (1997), 11(12), F95-F99
CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To assess the safety, efficacy and plasma drug levels of the combination of ritonavir plus saquinavir for the treatment of advanced HIV infection. Multicentre pilot study. Eighteen protease inhibitor-naive patients, with intolerance or contraindication to reverse transcriptase inhibitors, a median CD4 cell count of 12 .times. 106/l (range, 1-50 .times. 106/l), and a median HIV viremia of 5.25 log10 copies/mL (range, 4.00-6.13 log10 copies/mL). Patients received 600 mg twice daily of both ritonavir and saquinavir. Viremia was measured at baseline and at weeks 5, 9 and 13. Response was defined as a drop of viremia of more than 1 log10 at week 5. Plasma drug levels were detd. after at least 3 wk of combined treatment: samples were collected before and 1, 2, and 4 h after the morning ingestion of both drugs. The protease gene was sequenced at baseline and under treatment. Among the 16 patients evaluable at week 5, 11 were responders, and among these patients, six remained responders at week 13 (two with undetectable viremia). Study discontinuations were due to side-effects (n = 4), patient choice (n = 3), protocol violation (n = 1) and death (n = 1). Responders had higher drug levels than non-responders ($P < 0.01$ for saquinavir, $P = 0.04$ for ritonavir). In two non-responders, development of multiple new mutations at positions 10, 20, 48, 82, 84 and 90 was obsd. after 5-13 wk. The response to ritonavir plus saquinavir in advanced HIV infection is unpredictable. A minority of patients respond with disappearance of HIV viremia. In other patients, rapid cumulative emergence of protease mutations conferring resistance to treatment cannot always be prevented by good compliance and relatively high plasma drug levels.

IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Ritonavir/saquinavir treatment of HIV infection in humans)

L47 ANSWER 11 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:689271 CAPLUS
DOCUMENT NUMBER: 128:142
TITLE: Susceptibility of human immunodeficiency virus type 1 group O isolates to antiretroviral agents: in vitro phenotypic and genotypic analyses
AUTHOR(S): Descamps, Diane; Collin, Gilles; Letourneur, Franck; Apetrei, Cristian; Damond, Florence; Loussert-Ajaka, Ibtissam; Simon, Francois; Saragosti, Sentob;

Brun-Vezinet, Francoise
CORPORATE SOURCE: Laboratoire de Virologie, Hopital Bichat-Claude Bernard, Paris, 75018, Fr.
SOURCE: J. Virol. (1997), 71(11), 8893-8898
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors investigated the phenotypic and genotypic susceptibility of 11 human immunodeficiency virus type 1 (HIV-1) group O strains to nucleoside and nonnucleoside reverse transcriptase (RT) inhibitors and protease inhibitors in vitro. Phenotypic susceptibility was detd. by using a standardized in vitro assay of RT inhibition, taking into account the replication kinetics of each strain. HIV-1 group M and HIV-2 isolates were used as refs. DNA from cocultured peripheral blood mononuclear cells was amplified by using pol-specific group O primers and cloned for sequencing. Group O isolates were highly sensitive to nucleoside inhibitors, but six isolates were naturally highly resistant to all of the nonnucleoside RT inhibitors tested. Phylogenetic anal. of the pol gene showed that these isolates formed a sep. cluster within group O, and genotypic anal. revealed a tyrosine-to-cysteine substitution at residue 181. Differences in susceptibility to saquinavir and ritonavir (RTV) were not significant between group O and group M isolates, although the 50% inhibitory concn. of RTV for group O isolates was higher than that for the HIV-1 subtype B strains. The study of HIV-1 group O susceptibility to antiretroviral drugs revealed that the viruses tested had specific phenotypic characteristics contrasting with the group M phenotypic expression.
IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(susceptibility of human immunodeficiency virus type 1 group O isolates to antiretroviral agents using in vitro phenotypic and genotypic analyses)

L47 ANSWER 12 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:660406 CAPLUS
DOCUMENT NUMBER: 127:326004
TITLE: Activities of the human immunodeficiency virus type 1 (HIV-1) protease inhibitor nelfinavir mesylate in combination with reverse transcriptase and protease inhibitors against acute HIV-1 infection in vitro
AUTHOR(S): Patick, A. K.; Boritzki, T. J.; Bloom, L. A.
CORPORATE SOURCE: Agouron Pharmaceuticals, Inc., San Diego, CA, 92121, USA
SOURCE: Antimicrob. Agents Chemother. (1997), 41(10), 2159-2164
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Nelfinavir mesylate (formerly AG1343) is a potent and selective, nonpeptidic inhibitor of human immuno-deficiency virus type 1 (HIV-1) protease that was discovered by protein structure-based design methodologies. The authors evaluated the antiviral and cytotoxic effects of two-drug combinations of nelfinavir with the clin. approved antiretroviral therapeutics zidovudine (ZDV), lamivudine (3TC), dideoxycytidine (ddC; zalcitabine), stavudine (d4T), didanosine (ddI), indinavir, saquinavir, and ritonavir and a three-drug combination of nelfinavir with ZDV and 3TC against an acute HIV-1 strain RF infection of CEM-SS cells in vitro. Quant. assessment of drug interaction was evaluated by a universal response surface approach (W. R. Greco, G. Bravo, and J. C. Parsons, Pharm. Rev. 47:331-385, 1995) and by the method of M. N. Prichard and C. Shipman (Antiviral Res. 14:181-206, 1990). Both anal.

methods yielded similar results and showed that the two-drug combinations of nelfinavir with the reverse transcriptase inhibitors ZDV, 3TC, ddI, d4T, and ddC and the three-drug combination with ZDV and 3TC resulted in additive to statistically significant synergistic interactions. In a similar manner, the combination of nelfinavir with the three protease inhibitors resulted in additive (ritonavir and saquinavir) to slightly antagonistic (indinavir) interactions. In all combinations, minimal cellular cytotoxicity was obsd. with any drug alone and in combination. These results suggest that administration of combinations of the appropriate doses of nelfinavir with other currently approved antiretroviral therapeutic agents in vivo may result in enhanced antiviral activity with no assocd. increase in cellular cytotoxicity.

IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(activities of human immunodeficiency virus type 1 (HIV-1) protease inhibitor nelfinavir mesylate in combination with reverse transcriptase and protease inhibitors against acute HIV-1 infection in vitro in human cells)

L47 ANSWER 13 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:656512 CAPLUS
DOCUMENT NUMBER: 127:314288
TITLE: Clinical pharmacology of HIV protease inhibitors: focus on saquinavir, indinavir, and ritonavir
AUTHOR(S): Hoetelmans, R. M. W.; Meenhorst, P. L.; Mulder, J. W.; Burger, D. M.; Koks, C. H. W.; Beijnen, J. H.
CORPORATE SOURCE: Clinical Pharmacology HIV Protease Inhibitors, Neth.
SOURCE: Pharm. World Sci. (1997), 19(4), 159-175
CODEN: PWSCED; ISSN: 0928-1231
PUBLISHER: Kluwer
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 99 refs. In this review the clin. pharmacol. of HIV protease inhibitors, a new class of antiretroviral drugs, is discussed. After considering HIV protease function and structure, the development of inhibitors of HIV protease is presented. Three protease inhibitors are reviewed in more detail: saquinavir, indinavir, and ritonavir. Clin. trial results with these agents are evaluated. Furthermore, adverse effects, resistance, dosage and administration, clin. pharmacokinetics, pharmacokinetic-pharmacodynamic relationships, and drug interactions are discussed.

IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(clin. pharmacol. of HIV protease inhibitors: focus on saquinavir, indinavir, and ritonavir)

L47 ANSWER 14 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:561815 CAPLUS
DOCUMENT NUMBER: 127:229266
TITLE: Differential inhibition of cytochrome P450 isoforms by the protease inhibitors, ritonavir, saquinavir and indinavir
AUTHOR(S): Eagling, V. A.; Back, D. J.; Barry, M. G.
CORPORATE SOURCE: Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, L69 3GE, UK
SOURCE: Br. J. Clin. Pharmacol. (1997), 44(2), 190-194
CODEN: BCPHBM; ISSN: 0306-5251
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim of this study is to compare the inhibitory potential of the HIV

protease inhibitors saquinavir, ritonavir and indinavir against CYP1A2, CYP2C9, CYP2E1 and CYP3A4 catalyzed metabolic reactions in human liver microsomes in vitro. Microsomes from six human livers were utilized in this study. The probe substrates were phenacetin (CYP1A2), tolbutamide (CYP2C9), chlorzoxazone (CYP2E1) and testosterone (CYP3A4). Metabolites were analyzed by high performance liq. chromatog. IC50 (concn. of inhibitor giving 50% decrease in enzyme activity) and, where appropriate, Ki values were calcd. Ritonavir was a very potent inhibitor of CYP3A4 mediated testosterone 6.beta.-hydroxylation (mean Ki=0.019.+-.0.004 .mu.M, mean.+-.s.d.; n=6) and also inhibited tolbutamide hydroxylation (IC50=4.2.+-.1.3 .mu.M, mean.+-.s.d.; n=6). Inhibition of phenacetin O-deethylation and chlorzoxazone 6-hydroxylation was negligible. Indinavir was an order-of-magnitude less potent in inhibiting CYP3A4 (Ki=0.17.+-.0.01 .mu.M) and did not produce appreciable inhibition of the CYP1A2, CYP2C9 or CYP2E1 catalyzed reactions. Saquinavir was the least potent CYP3A4 inhibitor (Ki=2.99.+-.0.87 .mu.M) and produced some inhibition of CYP2C9 (approx. 50% at 50 .mu.M). The HIV protease inhibitors have differential effects on CYP isoenzymes. There is obvious potential for clin. significant drug interactions particularly with ritonavir. Pharmacokinetic drug interaction studies are crucial to gain an overall understanding of the beneficial and potentially harmful effects of this important group of drugs.

IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(differential inhibition of cytochrome P 450 isoforms by protease inhibitors, ritonavir, saquinavir and indinavir)

L47 ANSWER 15 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:556668 CAPLUS
DOCUMENT NUMBER: 127:171157
TITLE: Regression of cytomegalovirus retinitis associated with protease-inhibitor treatment in patients with AIDS
AUTHOR(S): Reed, J. Brian; Schwab, Ivan R.; Gordon, Jody; Morse, Lawrence S.
CORPORATE SOURCE: Department Ophthalmology, University California, Davis, Sacramento, CA, USA
SOURCE: Am. J. Ophthalmol. (1997), 124(2), 199-205
CODEN: AJOPAA; ISSN: 0002-9394
PUBLISHER: Ophthalmic Publishing Co
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The ocular fundi were examd. in 4 patients with AIDS who were placed on highly active antiretroviral therapy consisting of 2 nucleoside analogs and a protease inhibitor. The combined treatment resulted in increased CD4+ T-lymphocyte counts and decreased load of human immunodeficiency virus (HIV-1). A prospective evaluation of the effect of these drugs on an active cytomegalovirus retinitis lesion was conducted. None of these patients received specific anticytomegalovirus medications. The av. basal CD4+ T-lymphocyte count was 33 cells/.mu.L, which increased to an av. of 118.5 cells/.mu.L. Av. basal plasma HIV-1 viral loads (HIV-1-RNA copies/mL) decreased by 1.46 log units. In 1 patient, posterior progression (border advancement toward the posterior pole) of a cytomegalovirus retinitis lesion decelerated over time and stopped. Three other patients on initial examn. had areas of retinal scarring consistent with healed cytomegalovirus retinitis. Thus, the addn. of an HIV-1 protease inhibitor in the treatment of AIDS may lead to complete regression of cytomegalovirus lesions without the use of specific anticytomegalovirus drugs. This effect may be related to reduced HIV-1 loads, a possible direct drug effect, an increase in CD4+ T-lymphocyte counts, or other changes in immune status.

IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: BAC (Biological activity or effector, except adverse); THU

(Therapeutic use); BIOL (Biological study); USES (Uses)
(cytomegalovirus retinitis in patients with AIDS treatment by)

L47 ANSWER 16 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:536450 CAPLUS
DOCUMENT NUMBER: 127:185417
TITLE: Drug interaction potential with inhibitors of HIV protease
AUTHOR(S): Van Cleef, Gwendolyn F.; Fisher, Evelyn J.; Polk, Ron E.
CORPORATE SOURCE: School of Pharmacy, Virginia Commonwealth University/Medical College of Virginia, Richmond, VA, 23298, USA
SOURCE: Pharmacotherapy (1997), 17(4), 774-778
CODEN: PHPYDQ; ISSN: 0277-0008
PUBLISHER: Pharmacotherapy Publications
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We conducted a retrospective chart review to est. the potential for drug interactions in subjects infected with the human immunodeficiency virus-1 when a protease inhibitor was added to existing therapy. Medical records of 50 patients in each of three immunol. strata (CD4 cell counts/.mu.l < 100, 100-199, 200-500) were randomly selected from records of all patients receiving care at the clinic; 114 records were evaluable. The probabilities of one interaction or more were 31%, 42%, and 77% of patients if treated with indinavir, saquinavir, and ritonavir, resp., across all CD4 groups; when the CD4 count was below 100 cells/.mu.l, the probabilities were 55%, 63%, and 93%. Many of these interactions, however, resulted from administration of rifabutin, a drug likely to decrease in importance as less toxic alternatives become more widely administered. The potential for drug interactions is high when starting protease inhibitor therapy, esp. in patients with low CD4 cell counts who receive ritonavir. Concurrent therapy must be evaluated before treatment, as many agents are either contraindicated or require dosage modification.
IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug interaction potential with inhibitors of HIV protease)

L47 ANSWER 17 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:337741 CAPLUS
DOCUMENT NUMBER: 127:12782
TITLE: Human immunodeficiency virus type 1 protease inhibitors
AUTHOR(S): Mcdonald, Cheryl K.; Kuritzkes, Daniel R.
CORPORATE SOURCE: Division of Infectious Diseases, University of Colorado Health Sciences Center, Denver, USA
SOURCE: Arch. Intern. Med. (1997), 157(9), 951-959
CODEN: AIMDAP; ISSN: 0003-9926
PUBLISHER: American Medical Association
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 86 refs. Until recently, treatment for human immunodeficiency virus type 1 (HIV-1) infection was limited to the use of nucleoside inhibitors of the viral enzyme reverse transcriptase. While these agents initially offered promise, they have only modest antiviral activity and the benefits of treatment are limited by the emergence of drug resistance and dose-limiting toxic effects.1,2 Development of more potent drugs that target different stages of the virus life cycle has thus been aggressively pursued. Efforts to develop inhibitors of HIV-1 protease have yielded a potent new class of compds. that suppress HIV-1 replication to an extent far greater than was previously attainable. Four protease inhibitors, saquinavir mesylate, ritonavir, nelfinavir, and indinavir sulfate, have been approved by the Food and Drug Administration.

Other agents are undergoing active investigation. The purpose of this article is to review the currently available data on those agents that have been approved for clin. use.

IT **149845-06-7**, Saquinavir mesylate **155213-67-5**, Ritonavir
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HIV-1 protease inhibitors design and antiviral activity)

L47 ANSWER 18 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:333273 CAPLUS
DOCUMENT NUMBER: 127:44485
TITLE: The thiocarboxanilides UC-10 and UC-781 have an additive inhibitory effect against human immunodeficiency virus type 1 reverse transcriptase and replication in cell culture when combined with other antiretroviral drugs
AUTHOR(S): Balzarini, J.; De Clercq, E.
CORPORATE SOURCE: Rega Inst. Medical Res., Katholieke Univ. Leuven, Louvain, B-3000, Belg.
SOURCE: Antiviral Chem. Chemother. (1997), 8(3), 197-204
CODEN: ACCHEH; ISSN: 0956-3202
PUBLISHER: International Medical Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The thiocarboxanilides represent a structural class of potent and selective human immunodeficiency virus type 1 (HIV-1)-specific reverse transcriptase (RT) inhibitors. Combinations of the clin. candidate thiocarboxanilides UC-10 (oxime ether deriv.) and UC-781 (pentenyloxy ether deriv.) with a variety of nucleoside RT inhibitors (NRTIs) and non-nucleoside RT inhibitors (NNRTIs), two HIV protease inhibitors and one fusion/uncoating inhibitor were evaluated for their inhibitory effects on HIV-1 RT activity and HIV-1 replication in CEM cell cultures. The inhibitory activity of the NNRTIs including UC-10, UC-781, nevirapine, BHAP, .alpha.-APA, 8-chloro-TIBO, MKC-442 and the quinoxaline HBY 097 against HIV-1 RT was highly dependent on the nature of the template/primer used in the HIV-1 RT reaction. However, fractionary inhibitory concn. (FIC) indexes for all drug concns. evaluated in the combination expts. of UC_781 and the other NNRTIs fell within the range 0.5-1.5. This points to a predominantly additive effect of the thiocarboxanilides and other NNRTIs in the inhibition of HIV-1 RT. Similar FIC indexes were obsd. for the combination of UC-781 with the NRTI triphosphates AZT-TP, d4T-TP, ddCTP, ddATP and 3TC-TP and the NRTI diphosphate PMEApp against HIV-1 RT. All these drug combinations showed similar additive inhibitory effects on HIV-1 replication in cell culture. Also, the combinations of UC-10 or UC-781 with the protease inhibitors Ro31-8959/008 and ABT 84538.0 and the fusion/uncoating inhibitor bicyclam JM 3100 showed an additive effect (FIC within the 0.5-1.5 range). Thus, irresp. of the nature of the drugs, their combination with the thiocarboxanilides proved merely additive. In no case were antagonistic anti-HIV activity or increased cytotoxicity obsd. In conclusion, thiocarboxanilides combined with a variety of clin. used anti-HIV agents result in additive anti-HIV activity.

IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(UC-10 and UC-781 have additive inhibitory effect against HIV-1 reverse transcriptase and replication in cell culture when combined with other antiretroviral drugs)

L47 ANSWER 19 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:306377 CAPLUS
DOCUMENT NUMBER: 126:338434
TITLE: In vitro effect of .alpha.1-acid glycoprotein on the anti-human immunodeficiency virus (HIV) activity of

the protease inhibitor CGP 61755: a comparative study with other relevant HIV protease inhibitors
AUTHOR(S): Lazdins, Janis K.; Mestan, Jurgen; Goutte, Gerard; Walker, Maja R.; Bold, Guido; Capraro, Hans Georg; Klimkait, Thomas
CORPORATE SOURCE: CIBA-GEIGY Ltd., Pharmaceutical Research, Basel, Switz.
SOURCE: J. Infect. Dis. (1997), 175(5), 1063-1070
CODEN: JIDIAQ; ISSN: 0022-1899
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Protein binding can impair the potency of human immunodeficiency virus (HIV) protease inhibitors. Therefore, the activity of a novel compd., CGP 61755, was studied in the absence or presence of .alpha.1-acid glycoprotein (.alpha.1AGP). In MT-2 cells, the activity loss was 4-fold (EC90 without .alpha.1AGP, 29 nM vs. 122 nM with .alpha.1AGP). In primary lymphocytes, the loss was 8-fold (EC90, 45 nM vs. 364 nM). In identical expts., the activity loss in MT-2 cells and lymphocytes was 2- and 3-fold, resp., for indinavir, 11- and 10-fold for saquinavir, and 11- and 48-fold for ritonavir. For SC-52151, a 17-fold loss was seen in MT-2 cells, whereas no EC90 with .alpha.1AGP was reached in lymphocytes. This study demonstrates that the impact of .alpha.1AGP on in vitro activity varies greatly among different HIV protease inhibitors. The magnitude of such differences is greater in human lymphocytes than in a std. cell line.
IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir.
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of .alpha.1-acid glycoprotein on anti-HIV activity of protease inhibitor CGP 61755: comparative study with other relevant HIV protease inhibitors)

L47 ANSWER 20 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:249706 CAPLUS
DOCUMENT NUMBER: 126:287562
TITLE: Saquinavir pharmacokinetics alone and in combination with ritonavir in HIV-infected patients
AUTHOR(S): Merry, Concepta; Barry, Michael G.; Mulcahy, Fiona; Ryan, Mairin; Heavey, Jane; Tjia, John F.; Gibbons, Sara E.; Breckenridge, Alasdair M.; Back, David J.
CORPORATE SOURCE: Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, L69 3GE, UK
SOURCE: AIDS (London) (1997), 11(4), F29-F33
CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The most important hepatic enzyme involved in the metab. of protease inhibitors is cytochrome P 450 3A4 (CYP3A4). Ritonavir (RIT) is a potent inhibitor of CYP3A4 and inhibits saquinavir (SQV) metab. in healthy volunteers. In this study we investigated the kinetics of SQV when administered alone and in combination with RIT in HIV-infected patients. SQV pharmacokinetics were detd. in seven patients who had advanced HIV disease. Steady-state SQV profiles were obtained on two occasions following treatment with SQV 600 mg three times daily alone and when administered with RIT 300 mg twice daily. Blood samples were obtained at times 0, 1, 2, 4, 6 and 8 h post-dosing. Following centrifugation, sepd. plasma was heated at 58.degree.C for at least 30 min to inactivate HIV and stored at -80.degree.C until anal. using high performance liq. chromatog. For patients treated with SQV alone there was a 12-fold variability in the area under the SQV concn.-time curve (AUC0-8h) ranging from 293 to 3446 ng.cntdot.h/mL. When combined with RIT there was a marked increase in the max. plasma concn. of SQV [median (range), 146 (57-702) vs. 4795 (1420-15810) ng/mL; .apprx.95% confidence interval (CI), 2988-6819; P =

0.0006, Mann-Whitney U test]. The AUC0-8h for SQV was also significantly increased in the presence of RIT [median (range), 470 (293-3446) vs. 27 458 (7357-108 001) ng.cntdot.h/mL; .apprx.95% Cl, 16 628-35 111; P = 0.0006]. For some patients, administration of SQV 600 mg three times daily results in very low SQV plasma levels and possibly little antiviral effect. Combination of SQV with RIT results in a significant drug interaction mediated by enzyme inhibition which exposes patients to very high SQV concns. and potential toxicity. If combination therapy with SQV plus RIT is considered then the dose of SQV should be greatly reduced.

IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(saquinavir pharmacokinetics alone and in combination with ritonavir in HIV-infected human patients)

L47 ANSWER 21 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:243485 CAPLUS
DOCUMENT NUMBER: 126:327288
TITLE: Escape mutants of HIV-1 proteinase: enzymic efficiency and susceptibility to inhibition
AUTHOR(S): Wilson, Sara I.; Phylip, Lowri H.; Mills, John S.; Gulnik, Sergei V.; Erickson, John W.; Dunn, Ben M.; Kay, John
CORPORATE SOURCE: School of Molecular and Medical Biosciences, University of Wales College of Cardiff, P.O. Box 911, Cardiff, UK
SOURCE: Biochim. Biophys. Acta (1997), 1339(1), 113-125
CODEN: BBACAQ; ISSN: 0006-3002
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Genes encoding a no. of mutants of HIV-1 proteinase were sub-cloned and expressed in E. coli. The proteinases contg. mutations of single residues (e.g., G48V, V82F, I84V and L90M) were purified and their catalytic efficiencies relative to that of wild-type proteinase were examd. using a polyprotein (recombinant HIV-1 gag) substrate and several series of synthetic peptides based on the -Hydrophobic*Hydrophobic-, -Arom.*Pro- and pseudo-sym. types of cleavage junction. The L90M proteinase showed only small changes, whereas the activity of the other mutant enzymes was compromised more severely, particularly towards substrates of the -Arom.*Pro- and pseudo-sym. types. The susceptibility of the mutants and the wild-type proteinase to inhibition by eleven different compds. was compared. The L90M proteinase again showed only marginal changes in its susceptibility to all except one of the inhibitors examd. The Ki values detd. for one inhibitor (Ro31-8959) showed that its potency towards the V82F, L90M, I84V and G48V mutant proteinases resp. was 2-, 3-, 17- and 27-fold less than against the wild-type proteinase. Several of the other inhibitors examd. form a systematic series with Ro31-8959. The inhibition consts. derived with these and a no. of other inhibitors, including ABT-538 and L-735,524, are used in conjunction with the data on enzymic efficiency to assess whether each mutation in the proteinase confers an advantage for viral replication in the presence of any given inhibitor.

IT **127779-20-8**, Ro31-8959 **136522-18-4**, Ro31-8875
155213-67-5, ABT-538
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(enzymic efficiency and susceptibility to inhibition of escape mutants of HIV-1 proteinase)

L47 ANSWER 22 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:228825 CAPLUS
DOCUMENT NUMBER: 126:301431
TITLE: New drugs - Reports of new drugs recently approved by Searched by Edward Hart 305-9203

the FDA: ritonavir
AUTHOR(S): Ohta, Yukari; Shinkai, Ichiro
CORPORATE SOURCE: Banyu Clinical Research, Tokyo, Japan
SOURCE: Bioorg. Med. Chem. (1997), 5(3), 461-462
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Ritonavir (Norvir, A 84538, or ABT 538) is a peptidomimetic inhibitor of both HIV-1 and HIV-2 proteases. The concn. of drug that inhibits 50% of viral replication (EC50) ranged from 3.8 to 153 nM depending upon the HIV-1 isolate and the cells employed. The av. EC50 for low passage clin. isolates was 22 nM. In a 1090-patient study, 1.2 g of the drug used concomitantly with existing nucleoside therapy, produced a significant decrease in mean viral RNA levels of placebo and an increase in av. change of CD4 count over the first 16 wk. After seven months the mortality rate was 4.8% for ritonavir patients and 8.4% for placebo. Ritonavir demonstrated additive effects against HIV-1 in combination with either zidovudine (ZDV) or didanosine (ddI). Genotypic anal. of HIV-1 isolates with reduced susceptibility to ritonavir showed mutations in the HIV protease gene at amino acid positions 84 (Ile to Val), 82 (Val to Phe), 71 (Ala to Val), and 46 (Met to Ile). Phenotypic and genotypic changes in HIV isolates from selected patients treated with ritonavir were monitored in phase I/II trials over a period of 3-32 wk. Mutation appeared to occur in a stepwise and ordered fashion. The potential for HIV cross-resistance between protease inhibitors has not been fully explored. The abs. bioavailability of ritonavir has not been detd. After a 600 mg dose of oral soln., peak concns. of ritonavir were achieved approx. 2 and 4 h after dosing under fasting and nonfasting conditions, resp. The isopropylthiazole oxidn. metabolite (M-2) is the major metabolite. Studies utilizing human liver microsome have demonstrated that cytochrome P 450 3A (CYP3A) is the major isoform involved in ritonavir metab., although CYP2D6 also contributes to the formation of M-2. Agents that increase CYP3A activity would be expected to increase the clearance of ritonavir resulting in decrease of ritonavir plasma concn. Ritonavir can produce a large increase in plasma concns. of certain highly metabolized drugs. Ritonavir prevents fast metab. of saquinavir allowing increased blood levels. Addn. of saquinavir is not expected to accelerate resistance to ritonavir due to the distinct mutation profiles of both drugs. Norvir capsules are available for oral administration in a strength of 100 mg ritonavir. Norvir oral soln. is also available for oral administration as 80 mg/mL of ritonavir in a flavored vehicle.

IT **155213-67-5**, Ritonavir
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(antiviral ritonavir as peptidomimetic inhibitor of HIV-1 and HIV-2 proteases)

IT **127779-20-8**, Saquinavir
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metab., ritonavir prevention of; antiviral ritonavir as peptidomimetic inhibitor of HIV-1 and HIV-2 proteases)

L47 ANSWER 23 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:156459 CAPLUS
DOCUMENT NUMBER: 126:258416
TITLE: Pharmacokinetic enhancement of inhibitors of the human immunodeficiency virus protease by coadministration with ritonavir
AUTHOR(S): Kempf, Dale J.; Marsh, Kennan C.; Kumar, Gondi; Rodrigues, A. David; Denissen, Jon F.; McDonald, Edith; Kukulka, Michael J.; Hsu, Ann; Granneman, G. Richard; Baroldi, Paolo A.; Sun, Eugene; Pizzuti, David; Plattner, Jacob J.; Norbeck, Daniel W.;

Leonard, John M.
CORPORATE SOURCE: Dep. Infectious Diseases Res., Abbott Lab., Abbott Park, IL, 60064, USA
SOURCE: Antimicrob. Agents Chemother. (1997), 41(3), 654-660
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Coadministration with the human immunodeficiency virus (HIV) protease inhibitor ritonavir was investigated as a method for enhancing the levels of other peptidomimetic HIV protease inhibitors in plasma. In rat and human liver microsomes, ritonavir potently inhibited the cytochrome P 450 (CYP)-mediated metab. of saquinavir, indinavir, nelfinavir, and VX-478. The structural features of ritonavir responsible for CYP binding and inhibition were examd. Coadministration of other protease inhibitors with ritonavir in rats and dogs produced elevated and sustained plasma drug levels 8 to 12 h after a single dose. Drug exposure in rats was elevated by 8- to 46-fold. A >50-fold enhancement of the concns. of saquinavir in plasma was obsd. in humans following a single co-dose of ritonavir (600 mg) and saquinavir (200 mg). These results indicate that ritonavir can favorably alter the pharmacokinetic profiles of other protease inhibitors. Combination regimens of ritonavir and other protease inhibitors may thus play a role in the treatment of HIV infection. Because of potentially substantial drug level increases, however, such combinations require further investigation to establish safe regimens for clin. use.
IT **144142-67-6 155213-67-5**, A 152184
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); BIOL (Biological study); PROC (Process)
(cytochrome P 450 inhibition by; pharmacokinetic enhancement of inhibitors of human immunodeficiency virus protease by coadministration with ritonavir in relation to metab. by cytochrome P 450)
IT **127779-20-8**, Saquinavir
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(pharmacokinetic enhancement of inhibitors of human immunodeficiency virus protease by coadministration with ritonavir in relation to metab. by cytochrome P 450)

L47 ANSWER 24 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:21630 CAPLUS
DOCUMENT NUMBER: 126:112776
TITLE: Mutational anatomy of an HIV-1 protease variant conferring cross-resistance to protease inhibitors in clinical trials. Compensatory modulations of binding and activity
AUTHOR(S): Schock, Hilary B.; Garsky, Victor M.; Kuo, Lawrence C.
CORPORATE SOURCE: Dep. Antiviral Res., Merck Res. Lab., West Point, PA, 19486, USA
SOURCE: J. Biol. Chem. (1996), 271(50), 31957-31963
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Site-specific substitutions of as few as four amino acids (M46I/L63P/V82T/I84V) of the human immunodeficiency virus type 1 (HIV-1) protease engenders cross-resistance to a panel of protease inhibitors that are either in clin. trials or have recently been approved for HIV therapy (Condra, J. H., Schleif, W. A., Blahy, O. M., Gadryelski, L. J., Graham, D. J., Quintero, J. C., Rhodes, A., Robbins, H. L., Roth, E., Shivaprakash, M., Titus, D., Yang, T., Teppler, H., Squires, K. E., Deutsch, P. J., and Emini, E. A. (1995) Nature 374, 569-571). These four substitutions are among the prominent mutations found in primary HIV isolates obtained from patients undergoing therapy with several protease inhibitors. Two of these mutations (V82T/I84V) are located in, while the

other two (M46I/L63P)are away from, the binding cleft of the enzyme. The functional role of these mutations has now been delineated in terms of their influence on the binding affinity and catalytic efficiency of the protease. The authors have found that the double substitutions of M46I and L63P do not affect binding but instead endow the enzyme with a catalytic efficiency significantly exceeding (110-360%) that of the wild-type enzyme. In contrast, the double substitutions of V82T and I84V are detrimental to the ability of the protease to bind and, thereby, to catalyze. When combined, the four amino acid replacements institute in the protease resistance against inhibitors and a significantly higher catalytic activity than one contg. only mutations in its active site. The results suggest that in raising drug resistance, these four site-specific mutations of the protease are compensatory in function; those in the active site diminish equil. binding(by increasing Ki), and those away from the active site enhance catalysis (by increasing kcat/KM). This conclusion is further supported by energy ests. in that the Gibbs free energies of binding and catalysis for the quadruple mutant are quant. dictated by those of the double mutants.

IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(mutational anatomy of HIV-1 protease variant conferring cross-resistance to protease inhibitors in clin. trials in relation to compensatory modulations of binding and activity)

L47 ANSWER 25 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:21283 CAPLUS
DOCUMENT NUMBER: 126:112768
TITLE: Human immunodeficiency virus. Mutations in the viral protease that confer resistance to saquinavir increase the dissociation rate constant of the protease-saquinavir complex
AUTHOR(S): Maschera, Barbara; Darby, Graham; Palu, Giorgio; Wright, Lois L.; Tisdale, Margaret; Myers, Richard; Blair, Edward D.; Furfine, Eric S.
CORPORATE SOURCE: Dep. of Molecular Biochemistry, Glaxo Wellcome, Research Triangle Park, NC, 27709, USA
SOURCE: J. Biol. Chem. (1996), 271(52), 33231-33235
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mutations in the human immunodeficiency virus (HIV) protease (L90M, G48V, and L90M/G48V) arise when HIV is passaged in the presence of HIV protease inhibitor saquinavir. These mutations yield a virus with less sensitivity to the drug (L90M > G48V .mchgt. L90M/G48V). L90M, G48V, and L90M/G48V proteases have 1/20, 1/160, and 1/1000 the affinity for saquinavir compared to WT protease, resp. Therefore, the affinity of mutant protease for saquinavir decreased as the sensitivity of the virus to saquinavir decreased. Assocn. rate consts. for WT and mutant proteases with saquinavir were similar, ranging from 2 to 4.times.107 M-1 -1. In contrast, the dissocn. rate consts. for Wt, L90M, G48V, and L90M/G48V proteases complexed with saquinavir were 0.0014, 0.019, 0.128, and 0.54 s-1, resp. This indicated that the reduced affinity for mutant proteases and saquinavir is primarily the result of larger dissocn. rate consts. The increased dissocn. rate consts. may be the result of a decrease in the internal equil. between the bound inhibitor with the protease flaps up and the bound inhibitor with the flaps down. Interestingly, the affinity of these mutant proteases for VX-478, ABT-538, AG-1343, or L-735,524 was not reduced as much as that for saquinavir. Finally, the catalytic consts. of Wt and mutant proteases were detd. for eight small peptide substrates that mimic the viral cleavage sites in vivo. WT and L90M proteases had similar catalytic consts. for these substrates. In contrast, G48V and L90M/G48V

proteases had catalytic efficiency (kcat/Km) values with TLNF-PISP, RKIL-FLDG, and AETF-YVDG that were 1/10 to 1/20 the value of WT protease. The decreased catalytic efficiencies were primarily the result of increased Km values. Thus, mutations in the protease decrease the affinity of the enzyme for saquinavir and the catalytic efficiency with peptide substrates.

IT **127779-20-8**, Saquinavir **155213-67-5**, ABT-538
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(mutations in human immunodeficiency virus protease that confer resistance to saquinavir increase dissocn. rate const. of protease for saquinavir and other protease inhibitors in relation to catalytic efficiency and antiviral activity)

L47 ANSWER 26 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:693956 CAPLUS
DOCUMENT NUMBER: 126:139294
TITLE: HIV-Protease inhibitors. A new class of substances in antiretroviral therapy
AUTHOR(S): Mauss, S.; Seidlitz, B.; Jablonowski, H.; Haeussinger, D.
CORPORATE SOURCE: Klinik Gastroenterologie Hepatologie Infektiologie, Univ. Duesseldorf, Duesseldorf, D-40225, Germany
SOURCE: Dtsch. Med. Wochenschr. (1996), 121(44), 1369-1374
CODEN: DMWOAX; ISSN: 0012-0472
PUBLISHER: Thieme
DOCUMENT TYPE: Journal; General Review
LANGUAGE: German

AB A review with 33 refs. on the HIV-protease inhibitors saquinavir, ritonavir, and indinavir.

IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HIV protease inhibitors in antiretroviral therapy)

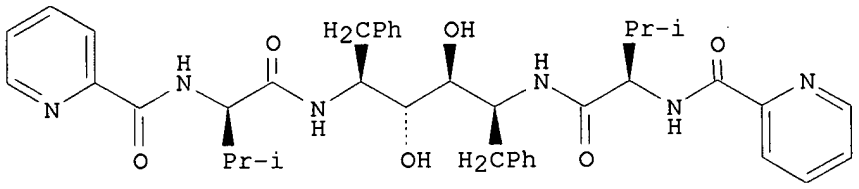
L47 ANSWER 27 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:642100 CAPLUS
DOCUMENT NUMBER: 125:315866
TITLE: Ritonavir
AUTHOR(S): Lea, Andrew P.; Faulds, Diana
CORPORATE SOURCE: Adis International Limited, Auckland, N. Z.
SOURCE: Drugs (1996), 52(4), 541-546
CODEN: DRUGAY; ISSN: 0012-6667
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with .apprx.37 refs. Ritonavir is a protease inhibitor with an HIV-1 resistance profile similar to that of indinavir, but different from that of saquinavir. Ritonavir has good oral bioavailability, and may increase the bioavailability of other protease inhibitors including saquinavir, nelfinavir, indinavir and VX-478. Clin. significant drug interactions have been predicted between ritonavir and a range of medications. In patients with HIV-1 infection, ritonavir markedly reduced viral load within 2 wk of treatment onset and also increased CD4+ cell counts. In a large placebo-controlled trial in patients with advanced HIV infection, the addn. of ritonavir to existing therapy reduced the risk of mortality by 43% and clin. progression by 56% after 6.1 mo. Triple therapy with ritonavir plus zidovudine, in combination with lamivudine or zalcitabine, reduced HIV viremia to below detectable levels in most patients with acute, and some patients with advanced HIV infection in 2 small trials. Early results suggest combination therapy with ritonavir and saquinavir increases CD4+ cell counts and decreases HIV RNA levels in patients with previously untreated HIV infection.

IT **127779-20-8**, Saquinavir **155213-67-5**, Ritonavir
RL: BAC (Biological activity or effector, except adverse); THU

(Therapeutic use); BIOL (Biological study); USES (Uses)
(a review of ritonavir in humans)

L47 ANSWER 28 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:124703 CAPLUS
DOCUMENT NUMBER: 124:196942
TITLE: Design, synthesis, and resistance patterns of MP-134 and MP-167, two novel inhibitors of HIV type 1 protease
AUTHOR(S): Mo, Hongmei; Markowitz, Martin; Majer, Pavel; Burt, Stanley K.; Gulnik, Sergei V.; Suvorov, Leonard I.; Erickson, John W.; Ho, David D.
CORPORATE SOURCE: School Medicine, New York University, New York, NY, 10016, USA
SOURCE: AIDS Res. Hum. Retroviruses (1996), 12(1), 55-61
CODEN: ARHRE7; ISSN: 0889-2229
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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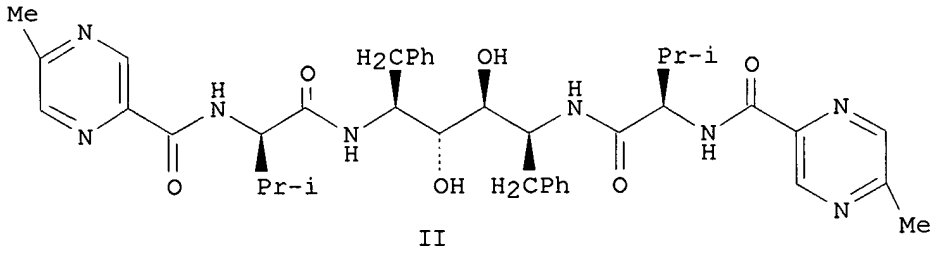

II

AB Inhibitors of HIV-1 protease represent a new class of antiretroviral compds. This report describes the design and synthesis of 2 novel C2 symmetry-based inhibitors, MP-134 (I) and MP-167 (II), specifically targeted against HIV-1 variants with reduced sensitivity to another related protease inhibitor, A-77003. In addn., the in vitro selection of viral variants with reduced sensitivity to these 2 protease inhibitors is described. An isoleucine-to-valine substitution at residue 84 (I84V) of the HIV-1 protease confers resistance to MP-134, whereas a glycine-to-valine substitution at residue 48 (G48V) confers resistance to MP-167. Testing other protease inhibitors against these variants has revealed specific overlapping patterns of resistance among these agents. These findings have important implications in the design of combination regimens using multiple protease inhibitors and underscore the need to develop non-cross-resistant compds. to be used toward this goal.

IT **127779-20-8**, Ro 31-8959 **155213-67-5**, ABT-538
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(design, synthesis, and resistance patterns of MP-134 and MP-167, two novel inhibitors of HIV type 1 protease)

L47 ANSWER 29 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:683314 CAPLUS
DOCUMENT NUMBER: 123:102100
TITLE: Kinetic Characterization and Cross-Resistance Patterns
Searched by Edward Hart 305-9203

Of HIV-1 Protease Mutants Selected under Drug Pressure
AUTHOR(S): Gulnik, Sergei V.; Suvorov, Leonid I.; Liu, Beishan; Yu, Betty; Anderson, Barry; Mitsuya, Hiroaki; Erickson, John W.
CORPORATE SOURCE: Frederick Cancer Research and Development Center, National Cancer Institute, Frederick, MD, 21702-1201, USA
SOURCE: Biochemistry (1995), 34(29), 9282-7
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Eleven different recombinant, drug-resistant HIV-1 protease (HIV PR) mutants-R8Q, V32I, M46I, V82A, V82F, V82I, I84V, V32I/I84V, M46I/V82F, M46I/I84V, and V321/K45I/F53L/A71V/I84V/L89M-were generated on the basis of results of in vitro selection expts. using the inhibitors A-77003, A-84538, and KNI-272. Kinetic parameters of mutant and wild-type (WT) enzymes were measured along with inhibition consts. (Ki) toward the inhibitors A-77003, A-84538, KNI-272, L-735,524, and Ro31-8959. The catalytic efficiency, kcat/Km, for the mutants decreased relative to WT by a factor of 1.2-15 and was mainly due to the elevation of Km. The effects of specific mutations on Ki values were unique with respect to both inhibitor and mutant enzyme. A new property, termed vitality, defined as the ratio (Kikcat/Km)mutant/(Kikcat/Km)WT was introduced to compare the selective advantage of different mutants to an inhibitor. High vitality values were generally obsd. with mutations that emerged during in vitro selection studies. The kinetic model along with the panel of mutants described here should be useful for evaluating and predicting patterns of resistance for HIV PR inhibitors and may aid in the selection of inhibitor combinations to combat drug resistance.

IT **127779-20-8 155213-67-5**, A 84538
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(kinetic characterization and cross-resistance patterns of HIV-1 protease mutants selected under drug pressure)

=> set hit rn

HIT RN IS NOT A VALID SET OPTION
For an explanation of the SET command, enter HELP SET at an arrow prompt (=>).

=> sel hit rn 1-29

E260 THROUGH E264 ASSIGNED

=> file reg

FILE 'REGISTRY' ENTERED AT 12:36:49 ON 06 NOV 2000

STRUCTURE FILE UPDATES: 5 NOV 2000 HIGHEST RN 301296-06-0
DICTIONARY FILE UPDATES: 5 NOV 2000 HIGHEST RN 301296-06-0

TSCA INFORMATION NOW CURRENT THROUGH July 8, 2000

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Structure search limits have been increased. See HELP SLIMIT for details.

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=> s e260-e264

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             1 127779-20-8/BI
               (127779-20-8/RN)
             1 136522-18-4/BI
               (136522-18-4/RN)
             1 144142-67-6/BI
               (144142-67-6/RN)
             1 149845-06-7/BI
               (149845-06-7/RN)
L48          5 (155213-67-5/BI OR 127779-20-8/BI OR 136522-18-4/BI OR 144142-67
               -6/BI OR 149845-06-7/BI)

=> d ide can 148 1-5


L48  ANSWER 1 OF 5  REGISTRY  COPYRIGHT 2000 ACS
RN   155213-67-5  REGISTRY
CN   2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-
     methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-
     bis(phenylmethyl)-, 5-thiazolylmethyl ester, (5S,8S,10S,11S)- (9CI)  (CA
     INDEX NAME)
OTHER CA INDEX NAMES:
CN   2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-
     methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-
     bis(phenylmethyl)-, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]-
OTHER NAMES:
CN   A 84538
CN   Abbott 84538
CN   ABT 538
CN   Norvir
CN   Ritonavir
FS   STEREOSEARCH
MF   C37 H48 N6 O5 S2
CI   COM
SR   CAS Registry Services
LC   STN Files:   ADISINSIGHT, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA,
       CAPLUS, CBNB, CEN, CIN, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU,
       DRUGUPDATES, EMBASE, IMSDIRECTORY, IPA, MRCK*, PHAR, PROMT, TOXLINE,
       TOXLIT, USAN, USPATFULL
         (*File contains numerically searchable property data)

Absolute stereochemistry.
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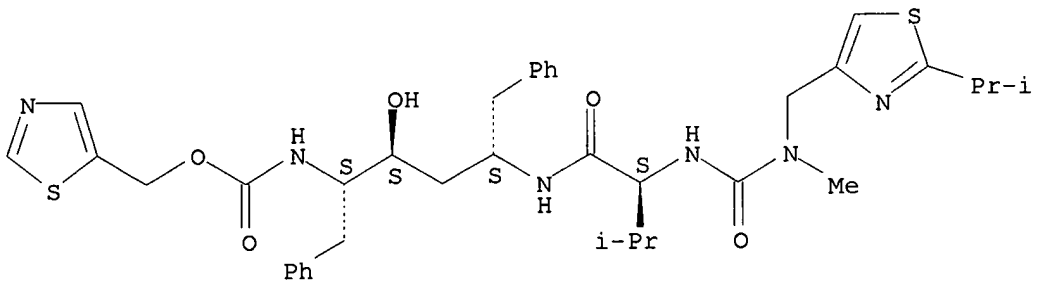


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Searched by Edward Hart 305-9203

REFERENCE 1: 133:275801

REFERENCE 2: 133:261126

REFERENCE 3: 133:247279

REFERENCE 4: 133:246744

REFERENCE 5: 133:232870

REFERENCE 6: 133:232803

REFERENCE 7: 133:232407

REFERENCE 8: 133:232406

REFERENCE 9: 133:232403

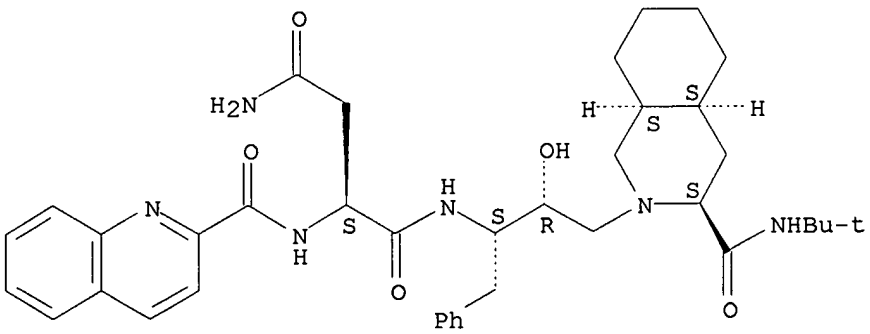
REFERENCE 10: 133:232402

L48 ANSWER 2 OF 5 REGISTRY COPYRIGHT 2000 ACS
RN **149845-06-7** REGISTRY
CN Butanediamide, N1-[(1S,2R)-3-[(3S,4aS,8aS)-3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-, (2S)-, monomethanesulfonate (salt) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Butanediamide, N1-[3-[3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-, [3S-[2[1R*(R*),2S*],3.alpha.,4a.beta.,8a.beta.]]-, monomethanesulfonate (salt)
OTHER NAMES:
CN Invirase
CN Ro 31-8959/003
CN Saquinavir mesylate
FS STEREOSEARCH
MF C38 H50 N6 O5 . C H4 O3 S
SR US Adopted Names Council
LC STN Files: ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CIN, DIOGENES, DRUGPAT, DRUGUPDATES, EMBASE, IPA, MRCK*, PROMT, TOXLINE, TOXLIT, USAN, USPATFULL
(*File contains numerically searchable property data)

CM 1

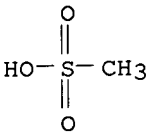
CRN 127779-20-8
CMF C38 H50 N6 O5

Absolute stereochemistry.



CM 2

CRN 75-75-2
CMF C H4 O3 S



20 REFERENCES IN FILE CA (1967 TO DATE)
20 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:247279

REFERENCE 2: 133:114641

REFERENCE 3: 133:114640

REFERENCE 4: 133:48892

REFERENCE 5: 132:352879

REFERENCE 6: 132:245879

REFERENCE 7: 132:193266

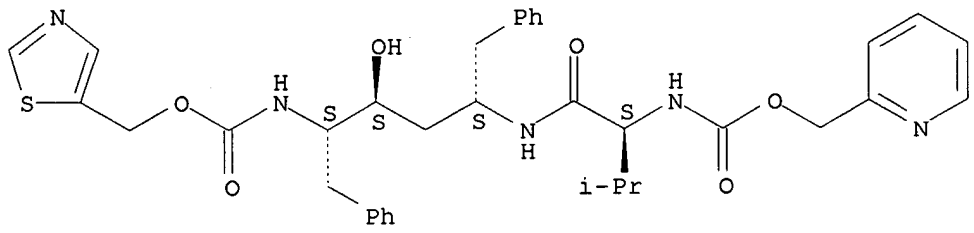
REFERENCE 8: 132:112920

REFERENCE 9: 132:54878

REFERENCE 10: 131:295035

L48 ANSWER 3 OF 5 REGISTRY COPYRIGHT 2000 ACS
RN **144142-67-6** REGISTRY
CN 2-Oxa-4,7,12-triazatridecan-13-oic acid, 10-hydroxy-5-(1-methylethyl)-3,6-dioxo-8,11-bis(phenylmethyl)-1-(2-pyridinyl)-, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C35 H41 N5 O6 S
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

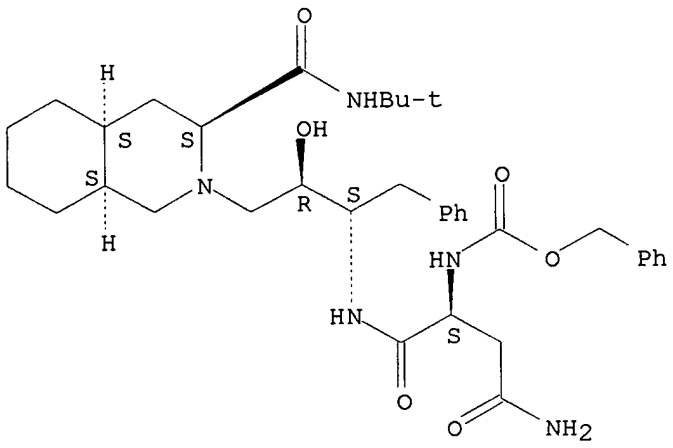
REFERENCE 1: 128:162539

REFERENCE 2: 126:258416

REFERENCE 3: 118:192283

L48 ANSWER 4 OF 5 REGISTRY COPYRIGHT 2000 ACS
RN **136522-18-4** REGISTRY
CN Carbamic acid, [(1S)-3-amino-1-[[[(1S,2R)-3-[(3S,4aS,8aS)-3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]amino]carbonyl]-3-oxopropyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Carbamic acid, [3-amino-1-[[[3-[3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]amino]carbonyl]-3-oxopropyl]-, phenylmethyl ester, [3S-[2[1R*(R*),2S*],3.alpha.,4a.beta.,8a.beta.]]-
OTHER NAMES:
CN Ro 31-8875
FS STEREOSEARCH
MF C36 H51 N5 O6
SR CA
LC STN Files: CA, CAPLUS, CASREACT, TOXLIT, USPATFULL

Absolute stereochemistry.



11 REFERENCES IN FILE CA (1967 TO DATE)
11 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:125399

REFERENCE 2: 126:327288

REFERENCE 3: 126:114991

REFERENCE 4: 122:230127

REFERENCE 5: 122:133857

REFERENCE 6: 121:281109

REFERENCE 7: 121:231363

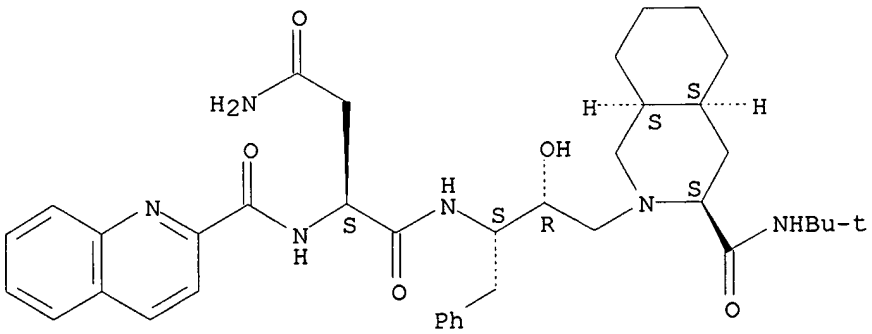
REFERENCE 8: 120:289408

REFERENCE 9: 116:120368

REFERENCE 10: 115:256637

L48 ANSWER 5 OF 5 REGISTRY COPYRIGHT 2000 ACS
RN **127779-20-8** REGISTRY
CN Butanediamide, N1-[(1S,2R)-3-[(3S,4aS,8aS)-3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-, (2S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Butanediamide, N1-[3-[3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-, [3S-[2[1R*(R*),2S*],3.alpha.,4a.beta.,8a.beta.]]-
OTHER NAMES:
CN (S)-N-[(.alpha.S)-.alpha.-[(1R)-2-[(3S,4aS,8aS)-3-(tert-Butylcarbamoyl)octahydro-2(1H)-isoquinolyl]-1-hydroxyethyl]phenethyl]-2-quinaldamidosuccinamide
CN Fortovase
CN Ro 31-8959
CN Ro 31-8959/000
CN Saquinavir
CN Sch 52852
FS STEREOSEARCH
DR 131176-13-1
MF C38 H50 N6 O5
CI COM
SR CA
LC STN Files: ADISINSIGHT, AIDSLINE, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CIN, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IMSDIRECTORY, IPA, MEDLINE, MRCK*, PHAR, PROMT, TOXLINE, TOXLIT, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry.



491 REFERENCES IN FILE CA (1967 TO DATE)
7 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
495 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:275801

REFERENCE 2: 133:261126

REFERENCE 3: 133:256870

REFERENCE 4: 133:247279

REFERENCE 5: 133:246744

REFERENCE 6: 133:232870

REFERENCE 7: 133:232803

REFERENCE 8: 133:232403

REFERENCE 9: 133:232402

REFERENCE 10: 133:232401